January 1986 Vol 55 No 1

CUK-H05916-K-P2573

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# British Heart Journal

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*monthly journal of cardiology*
*blished in association with*
*e British Cardiac Society*

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**British Medical Association**

ASTM CODEN: BHJUAV 55(1) 1—116 (1986)
ISSN 0007-0769

# British Heart Journal

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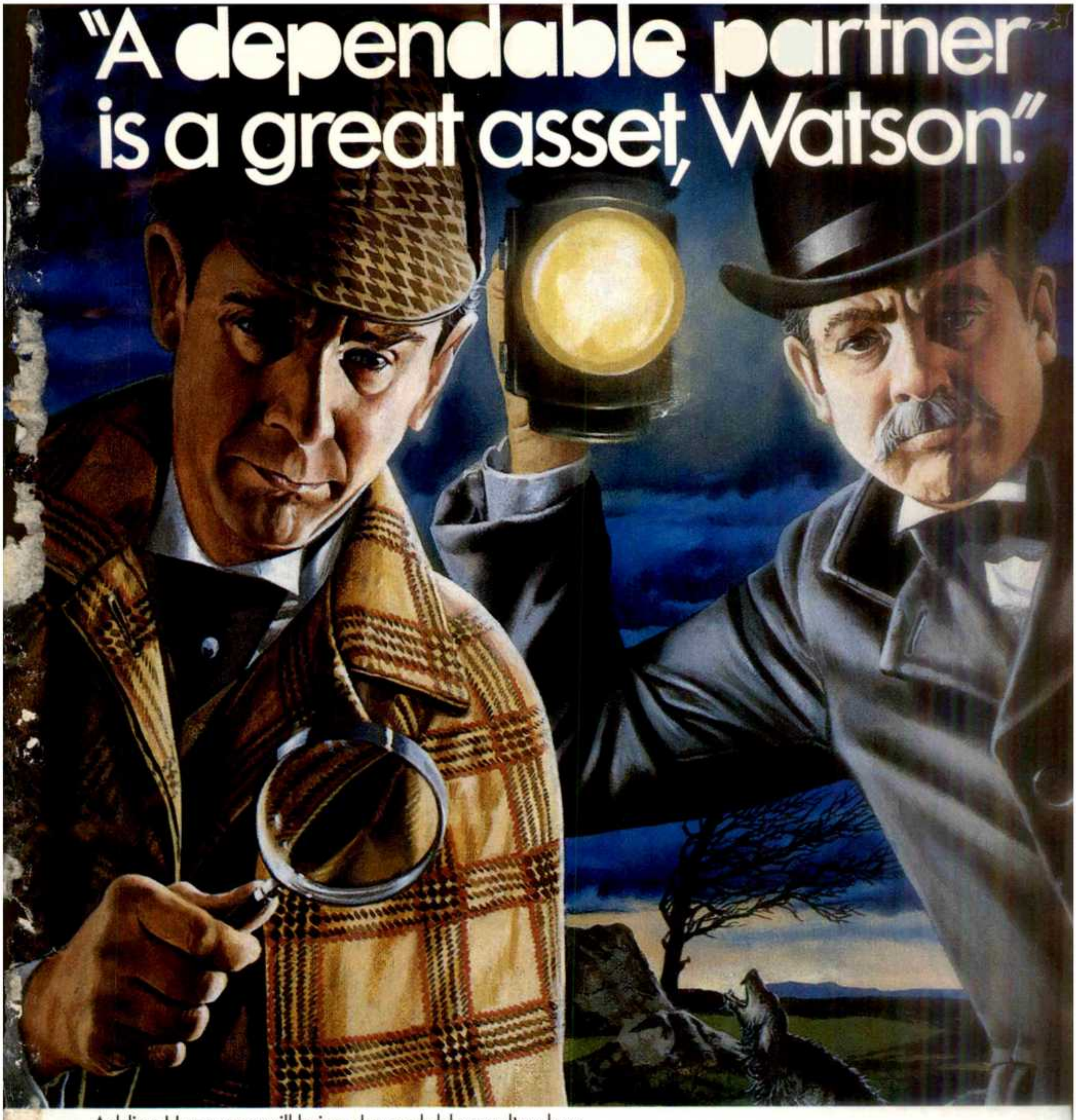
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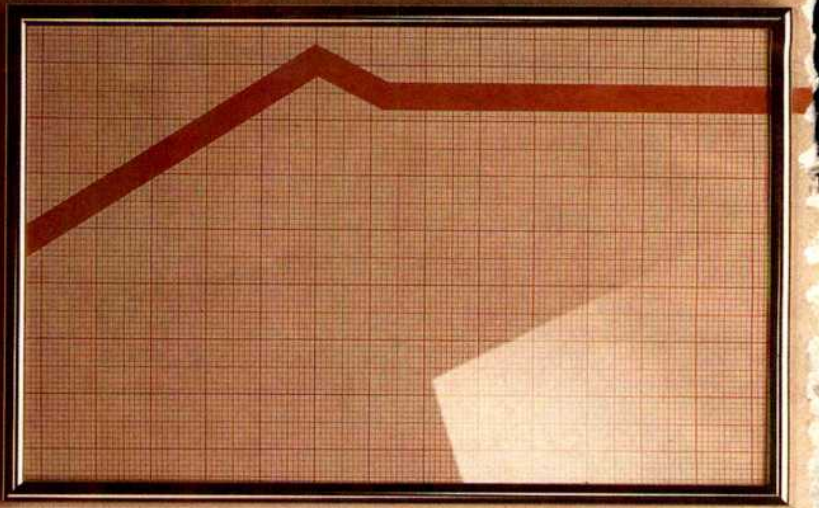

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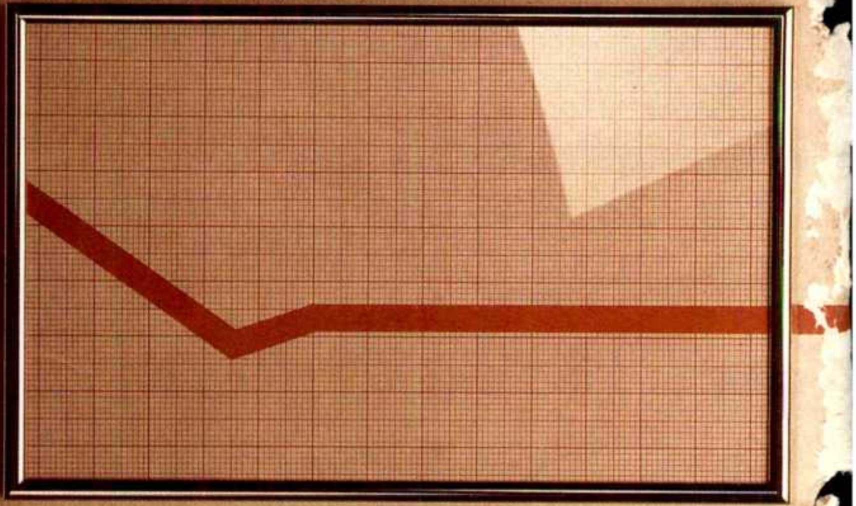

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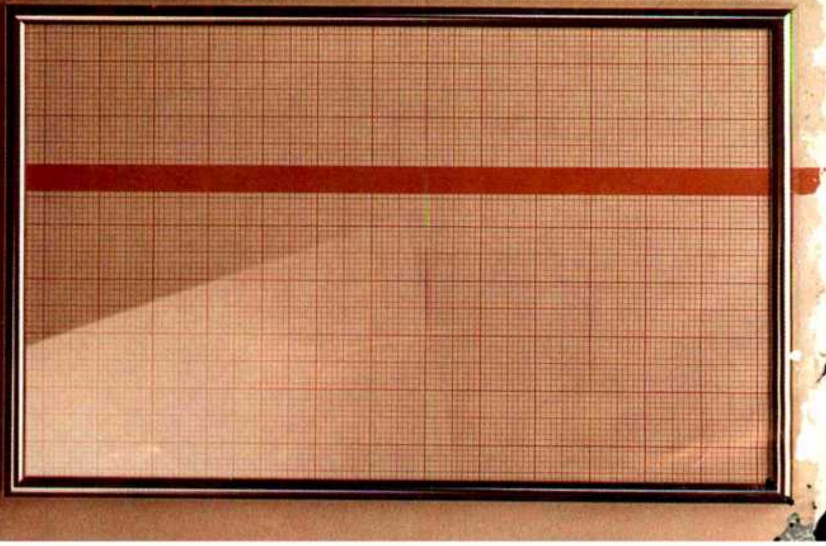

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**References**
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2. Gomez, H. J., *et al., Journal of Hypertension* (in press).
3. Kjekshus, J. K., *Scandinavian Journal of Urology and Nephrology,* 1984, Suppl. 79, p.115.

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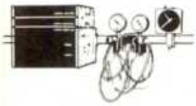
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*Br Heart J* 1986; **55**: 1–3

# *Editorial*

# Surgical management of the neonate with congenital heart disease

MARC R DE LEVAL

*From the Thoracic Unit, The Hospital for Sick Children, Great Ormond Street, London*

Despite the multiplication of specialised centres and a fall in the birth rate, paediatric cardiac units have seen a steady increase in the number of infants with congenital heart defects operated on during the neonatal period. This changing pattern is the result of continuing advances in neonatology, early detection and better management of the neonate with a congenital heart defect, and the tendency, rightly or wrongly, to operate on more complex defects.

Advances in neonatology with improved infant care and ventilatory support for infants with respiratory distress syndrome have increased the neonatal survival rate. Hence the increase in the number of premature infants with a persistent ductus ateriosus who require surgical closure, often after a trial of treatment with indomethacin.

More specifically the preoperative status of neonates with congenital heart defects has been greatly improved by the introduction of prostaglandins and a trend to non-invasive diagnosis. Conventional clinical diagnosis of congenital heart defects by physical examination, chest radiography, and electrocardiography is often unreliable, particularly in the neonatal period. For this reason cardiac catheterisation and angiocardiography have for many years been the standard diagnostic methods in this age group. Cross sectional echocardiography has changed the indications and need for cardiac catheterisation. Neonates have a technically excellent subcostal and suprasternal window that allows good definition of the intracardiac anatomy. Most congenital cardiac malformations can be diagnosed by cross sectional echocardiography in the neonate. The anatomical definition of the anomaly together with the physical findings are often sufficient to proceed to surgical treatment in the absence of haemodynamic information from a cardiac catheterisation. We have operated on numerous neonates with various heart defects when all non-invasive investigations were typical of the suspected abnormality. The type of surgery to which the patient is to be submitted must also be considered in this decision. For example, the preoperative information required for a shunt procedure differs from that required for a complete repair. Is the risk of preoperative invasive investigation of a sick neonate justified by its greater accuracy compared with alternative non-invasive investigations? This question cannot be answered unless risk and accuracy can be expressed in the same units, for only then can they be usefully compared.

Pharmacological manipulation of the ductus arteriosus with prostaglandins has been a breakthrough in the management of cyanotic neonates with reduced pulmonary blood flow. Operations are now performed more electively and infants reach the operating theatre in a better condition, that is warm, well oxygenated, non-acidotic, and with a good cardiac output. Prostaglandins have been particularly beneficial for patients with pulmonary atresia with or without ventricular septal defect, for those with tricuspid atresia, and to some extent for those with transposition of the great arteries. They have also been used for aortic arch anomalies, coarctation of the aorta, or critical aortic valve stenosis in which part of the systemic circulation may depend on the patency of the ductus arteriosus. The exact mechanism by which prostaglandins afford haemodynamic improvement in patients with obstructive lesions of the systemic circulation is not completely understood except in conditions in which the systemic circulation is entirely duct dependent.

Refinements of well established surgical pro-

Requests for reprints to Dr Marc R de Leval, Thoracic Unit, The Hospital for Sick Children, Great Ormond Street, London WC1N 3JH.

cedures and their implementation as logical management protocols have also contributed to changes in neonatal cardiac surgery. The management of neonatal coarctation of the aorta and critical aortic stenosis may be taken as examples.

The acutely ill neonate with coarctation of the aorta requires urgent treatment. The prognosis is especially poor when the coarctation is associated with intracardiac anomalies, of which ventricular septal defect is the most common. In general these patients tend to have intractable heart failure, metabolic acidosis, and renal failure. Formerly we considered these two cardiac anomalies to be entities and we treated each one separately. The coarctation was repaired first and then, if the patient remained in intractable heart failure, the ventricular septal defect was repaired. Now we know that neonates with a large ventricular septal defect are more likely to survive if banding of the pulmonary artery is carried out as well as repair of the coarctation. Though it is not a panacea against late complications, the subclavian flap angioplasty technique to relieve coarctation of the aorta has been a useful additional surgical treatment.

Aortic valvar stenosis that is severe enough to produce left ventricular failure in the neonatal period is associated with a high mortality rate. Medical treatment is only briefly effective and surgical intervention is mandatory for survival. During the past five years we have evolved a protocol for these infants which includes a non-invasive diagnosis, followed by valvotomy without cardiopulmonary bypass. This is done either under inflow occlusion through a transaortic approach, or by transapical dilatation of the valve. We have a very limited experience with balloon dilatation of the aortic valve, but this procedure might become the method of choice for critical aortic stenosis in the neonate.

Open heart surgery during the neonatal period has made little advance during the past decade. Studies of biochemical and immunological reactions induced by extracorporeal circulation and a better understanding of the function and protection of the neonatal myocardium should lead to safer cardiac surgery. Repair of a total anomalous pulmonary venous connection is one of the commonest open heart procedures performed in the neonate. After the sharp reduction in the surgical mortality that followed the revival of deep hypothermia and circulatory arrest in the early 1970s the mortality for this condition remains greater than 30%. Patients under one week of age with obstruction of pulmonary venous return have a particularly poor prognosis. Intrinsic anomalies of the pulmonary veins and of the lung parenchyma may account for these disappointing results.

New trends in the management of complete transposition of the great arteries illustrate the impact made by innovative surgery. Though intra-atrial repair of transposition of the great arteries by either the Mustard or Senning techniques has been widely used for many years, there is concern about the very long term results of these interventions. Jatene and colleagues introduced the arterial switch or so called anatomical repair of transposition of the great arteries.[1] This was successfully applied to transposition with raised left ventricular pressure due to either a large left to right shunt or dynamic left ventricular outflow tract obstruction. The concept was more recently extended to the correction of simple transposition of the great arteries during the neonatal period at a time when the pulmonary vascular resistance is still so high that the left ventricle is capable of sustaining the systemic circulation after the switch procedure. The early results of this management have been very encouraging. The prospect of improved long term results would justify a wider use of this approach if late complications could be avoided. Because this remains a hypothetical prospect some units, such as ours, continue to be rather conservative about the management of simple transposition of the great arteries.

Progress in neonatology, the availability of reliable pharmacological and surgical means to regulate the pulmonary blood flow, and the fundamental demonstration that the pulmonary and the systemic circulations left in series could be successfully served by one ventricle (Fontan operation) have made the most complex cardiac malformations amenable to surgery. These developments account for changes in the management of hypoplastic right and left heart syndromes. The latter is the fourth most common congenital cardiac anomaly seen in infancy (after ventricular septal defect, tetralogy of Fallot, and transposition of the great arteries) and is responsible for nearly 25% of cardiac deaths during the first week of life. Closure of the arterial duct in the first few days of life explains the early death of so many neonates with hypoplastic left heart syndromes. On the assumption that hypoplastic left heart syndrome is very similar to extreme forms of right ventricular hypoplasia, tricuspid atresia, and other forms of univentricular hearts Norwood and his colleagues have developed palliative procedures for such patients.[2] The purpose of these interventions is to establish a permanent communication between the right ventricle and the aorta, regulate the pulmonary blood flow (avoiding pulmonary vascular changes secondary to increased flow and pressure), and to assure a satisfactory interatrial communication. The definitive repair consists of separating the systemic and pulmonary circulations by performing a Fontan type of procedure. We have followed with interest the evolution and the careful and systematic study of Norwood and his colleagues.[2] We believe that such a planned research programme should be supported but we think that it is premature for all surgical teams to embark on these often heroic surgical treatments without their knowing how many of the survivors of the first stage operation will eventually be suitable for a Fontan procedure. If their numbers are very small is it ethically justifiable to oblige patients who would otherwise have died as neonates to carry their handicap into childhood only to succumb because no further treatment is possible?

Neonatal cardiac transplantation with a homograft or even a xenograft heart is an alternative approach to treatment of patients with these complex malformations. Both procedures have already been performed. Are these pioneering endeavours going to open the doors to new hopes or create formidable problems?

One can predict that in the foreseeable future a number of researches that are currently underway will deeply influence the incidence and the management of neonates with congenital heart defects. Some workers are investigating the possibilities of operating on fetal hearts in utero because they consider that the womb is likely to be a better postoperative environment than the most advanced incubators. In several centres intrauterine echocardiographic diagnosis of complex cardiac malformations has led to the termination of pregnancy. In future the attitude towards the treatment of complex cardiac malformations in neonates will be based on the quality of adult life enjoyed by patients operated on today and on the outcomes of these two conflicting and radical tendencies, that is to replace the defective organ or to prevent the birth of the faulty embryo. Ethical, social, and economic considerations must also influence this subtle decision making.

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*Br Heart J* 1986; 55: 4–13

# Asynchronous left ventricular wall motion early after coronary thrombosis

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SUMMARY To study regional wall motion early in the development of acute myocardial infarction, left ventriculograms performed in 24 patients before thrombolysis and within 3·5 (1·2) (mean (SD)) hours of the onset of pain were digitised frame by frame. Isometric and contour plots of regional wall motion were constructed. In 19 patients (seven with anterior descending, eight with right, and four with circumflex disease) thrombosis was demonstrated on an underlying stenosis. In 10 patients the two remaining coronary arteries were normal, and in nine, one or both showed important disease. Mean values of global indices of left ventricular function, including end diastolic volume, ejection fraction, peak ejection and filling rates, and cavity shape changes were all within normal limits, though end systolic volume was significantly raised. Total systolic amplitude of wall motion was normal in the affected area in all but seven patients (four with anterior descending, two with right, and one with circumflex thrombosis). Dyskinesis of more than 2 mm was seen in only three patients, all with thrombosis of the anterior descending coronary artery, and hyperkinesis was present in four. The commonest abnormality of wall motion was hypokinesis during ejection followed by prolonged inward motion during isovolumic relaxation, which was seen in four patients with anterior descending, seven with right, and three with circumflex artery thrombosis. This was preceded by outward motion during isovolumic contraction and delayed inward motion during ejection in eight with right or circumflex thrombosis. Five of six patients without thrombosis had simple hypokinesis or dyskinesis without asynchrony. Disease of other coronary arteries did not affect the pattern of wall motion seen after right or circumflex coronary artery occlusion but it reduced the incidence of delayed inward motion along the free wall after thrombosis of anterior descending artery. Thus early after acute coronary thrombosis asynchronous wall motion is commoner than simple hypokinesis or dyskinesis. Its persistence suggests that in the setting of coronary artery thrombosis in man, residual contractile activity may persist for up to six hours after the onset of symptoms.

Selection of patients who are suitable for thrombolysis and acute revascularisation (for possible limitation of infarct size) is difficult.[1] [2] The aim is to identify those in whom there is important impairment of regional left ventricular function at a time when it is potentially reversible by re-establishment of coronary flow. Since myocardial function manifests itself in the amplitude and timing of wall motion, the present study was designed to examine left ventricular contrast angiograms of patients early after acute myocardial infarction with particular reference to detecting asynchronous regional wall movement. We hoped that this would provide a baseline for assessing the effects of procedures designed to limit infarct size and also that it would be possible to recognise patterns of motion which would identify regions where function was impaired but not irretrievably lost.

## Patients and methods

Twenty four patients (aged 38–72 years) who

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Accepted for publication 10 September 1985

fulfilled standard criteria as potential candidates for thrombolysis were studied at the University Hospital, Heidelberg.[3] The study was performed 3·5 (1·3) hours (mean (SD)) (range 0·5 to 7 hours) after the onset of symptoms. Left ventriculography was performed in the 30° right anterior oblique projection as part of the clinical study. An injection of 40 ml Urografin was given into the left ventricle at a flow rate of 12 ml/s through a pigtail catheter, and a cine film was exposed at 50 frames/s. Calibration was established from movement of the catheter tip positioned in the left ventricle when the table was displaced by 8 cm. Ectopic and postectopic beats were not studied. Multiple views of the coronary arteries were then obtained by means of Judkins' technique.

### ANALYSIS OF ANGIOGRAMS

Cavity outlines were digitised frame by frame over two beats in 18 of the patients and over a single beat for the remainder.[4] A fixed external reference point on the margin of the cine frame was used throughout. The timing of aortic valve opening and closure at the start and end of ejection was established from direct inspection of the angiogram, from the frame on which each of these movements was complete. The timing of mitral valve opening was taken as that of the frame in which unopacified blood first appeared within the left ventricular cavity at the onset of diastole. Left ventricular ejection was taken as the interval between aortic valve opening and closure, and isovolumic relaxation as that between aortic closure and mitral opening.

From the digitised data, plots were made of superimposed endocardial cavity outlines—those from the start of the beat to the outline with the smallest area being taken as systolic and the remainder as diastolic. For each frame cavity volume was calculated[5] and plotted as a continuous curve along with its first derivative from which peak rates of systolic and diastolic volume change were derived. The interval from mitral valve opening to the times of registration of peak filling rate and the end of rapid filling when the rate had dropped to 20% of its peak level was also noted. Shape index was calculated as $4\pi \times \text{area}/(\text{perimeter})^2$.[6] Ejection fraction was taken as stroke volume divided by end diastolic volume.

Regional wall motion was demonstrated by constructing isometric and contour plots for each beat.[4] The method depends on multiple plots of wall motion against time, derived from 40 equally spaced points around the circumference of the end diastolic frame starting from the junction of the mitral valve with the aortic root. Segments 1–15 thus represent the inferior wall, 1–5 being the mitral valve, 15–25 the apical region, and 25–40 the free wall of the left ventricle. Regional wall motion was analysed either by stacking these individual plots obliquely to give an isometric display, or by constructing a series of contours representing 1 mm of inward or outward movement of endocardium from its position in the end diastolic frame. Examples are given in Figs. 1–4. Results from the patients were compared with those from 20 normal subjects with chest pain, normal ventricular haemodynamics, and coronary arteriograms. From these displays, the following information was derived.

(*a*) Segments in which the overall amplitude of inward motion during systole lay outside the 95% confidence limit of normal for the region in question were identified. Overall systole was here taken as extending from the time of maximum cavity area to the onset of mitral valve opening at the start of ventricular filling. When the amplitude of motion was below the lower 95% limit, the region was regarded as showing hypokinesis, and when it was greater than the upper 95% limit as showing hyperkinesis. Wall motion during ejection was considered in the same way. Dyskinesis was taken as outward motion of 2 mm or more occurring during ejection, lasting for at least 100 ms. Specifically excluded from this definition was transient outward movement within 50 ms of aortic valve opening followed by inward motion later in ejection. This latter pattern was frequently seen in association with disturbances of isovolumic contraction.

(*b*) Segments showing abnormal wall motion early during systole. Two types were recognised. The first was abnormal (2 mm or more) outward movement of endocardium during isovolumic contraction and within the first 50 ms of ejection.[7] The second was significant (more than 3 mm) inward wall motion during isovolumic contraction.

(*c*) Segments showing abnormal inward movement during isovolumic relaxation of 2 or more mm.[3]

(*d*) Outward motion of 7 mm or more during isovolumic relaxation involving segments 25–40 along the free wall.[4]

The extent of each abnormality was determined from the number of segments for which values lay outside the 95% confidence limits of normal. To study regional velocity of wall motion individual plots were identified on the anterior wall, at the apex, and on the inferior wall and displayed separately along with their first differential with respect to time.[8] From this information the interval between maximum cavity area and peak rate of inward motion was plotted for each of the three segments together with the spread of values between them—that is the interval between the earliest and latest registration of the peak. Similarly, the timing of peak inward

Table *Overall left ventricular function*

| | *Group 1 (n=10)* | *Group 2 (n=9)* | *Group 3 (n=5)* | *Reproducibility* | *Normal (n=20)* |
|---|---|---|---|---|---|
| End diastolic volume (ml) | 190 (66) | 180 (55) | 190 (80) | 12 | 150 (35) |
| End systolic volume (ml) | 75 (28) | 70 (45) | 75 (80) | 6 | 32 (16) |
| Ejection fraction (%) | 64 (7) | 60 (12) | 65 (29) | 4 | 66 (7) |
| Peak ejection rate (ml/s) | 815 (240) | 560 (135) | 680 (190) | 110 | 580 (210) |
| Normalised ejection rate $s^{-1}$ | 3·9 (0·6) | 4·0 (1·5) | 3·8 (0·9) | 0·6 | 4·2 (1·1) |
| Peak filling rate (ml/s) | 890 (390) | 480 (180) | 800 (250) | 90 | 690 (260) |
| Normalised filling rate $s^{-1}$ | 4·2 (0·8) | 3·5 (1·6) | 4·4 (1·1)* | 0·5 | 4·2 (0·7) |
| Shape change (%) | 16 (7) | 13 (8) | 25 (11) | 3 | 22 (7) |

motion and the end of rapid outward motion when the velocity had fallen to 20% of its peak value were also measured for each segment with respect to the timing of mitral valve opening along with the spread of each between segments. Regions in which the overall amplitude of motion was 4 mm or less were not studied, because the first derivatives consistently failed to show the normal configuration during ejection and filling and these measurements could not be made.

### ANALYSIS OF CORONARY ARTERIOGRAMS

Coronary arteriograms were examined when the analysis of wall motion was complete. In 19 of the patients, one coronary artery was found to be completely obstructed. The cut off of contrast was sharp, and when streptokinase was infused a lumen was re-established. Such an obstruction was taken as being due to thrombus, and the affected artery was noted. The extent of the remaining coronary artery disease was also recorded. From this information it was possible to divide the patients into three groups: *group 1*—those in whom there was occlusion of a single coronary artery by thrombus, the other two vessels either being normal or showing no more than a trivial stenosis; *group 2*—those in whom there was occlusion of a single coronary artery by thrombus, but an important (more than 75%) lesion of one or both of the remaining arteries; and *group 3*—those in whom no thrombus could be identified but in whom coronary artery disease was present. Groups 1 and 2 were further subdivided according to which of the three main coronary arteries was affected by the thrombus.

### STATISTICAL METHODS

Student's $t$ test was used to compare differences

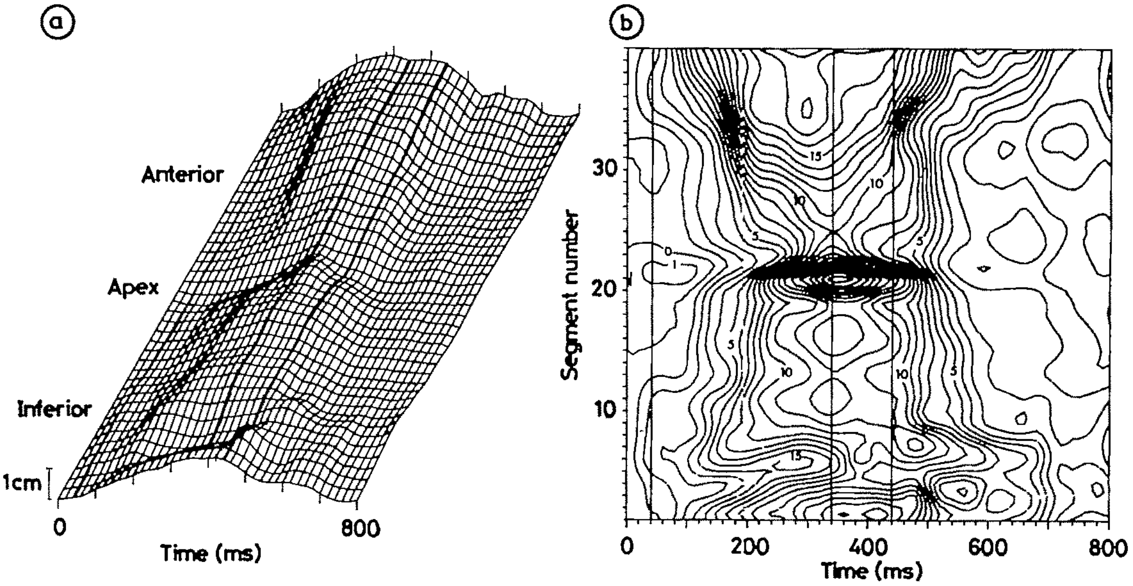

Fig. 1 *(a) Isometric plot of normal angiogram. Accentuated time markers (isochrones) represent aortic opening, aortic closure, and mitral opening, respectively. The pattern of wall motion is synchronous except in the most inferior segments where mitral valve motion is recorded. (b) Contour plot of data from Fig. 1a.*

between mean values. Reproducibility of measures of overall left ventricular function was established from measurements made in 18 patients in whom two beats were of adequate technical quality for digitisation; this was determined as the root mean square of the difference between the two determinations.

## Results

### DISTRIBUTION OF LESIONS

Thrombosis of one coronary artery was demonstrated in 19 patients. Ten of them had no important disease elsewhere in the coronary tree (group 1), the thrombosis being in the anterior descending in three, in the circumflex in two, and in the right coronary artery in five patients. Of the remainder, in whom there was important disease elsewhere (group 2), the thrombosis was in the anterior descending in four, the right in three, and the circumflex in two. In the remaining five patients, no clear thrombosis was demonstrated (group 3); however, important disease of anterior descending alone was present in three, anterior descending and circumflex in one, and left main stem disease in one.

### OVERALL LEFT VENTRICULAR FUNCTION

The Table gives measurements of overall left ventricular function for the three groups of patients together with normal values and estimates of reproducibility from paired determinations. Values of end systolic volume were significantly greater than normal in groups 1 and 2 ($p<0\cdot05$), but otherwise mean values did not differ significantly from normal, or from one another. In several cases, however, values outside the 95% confidence limits of normal were seen. These included seven in whom end diastolic volume was greater than the upper limit of normal, four in group 1, two in group 2, and one in group 3. End systolic volume lay outside the normal range in six cases in group 1, three in group 2, and one in group 3. Ejection fraction was below normal in only three patients, one in each group. Values of peak ejection were within the wide limits of normal in all patients, but peak normalised filling rate was low in four patients, three in group 2 and one in group 3; depression in group 2 was statistically significant compared with normal ($p<0\cdot05$). The extent of overall shape change during the cardiac cycle was also within normal limits in all except four patients, one in group 1 and three in group 2.

### REGIONAL LEFT VENTRICULAR FUNCTION

Fig. 1 gives examples of isometric and contour displays from a normal subject. On the isometric

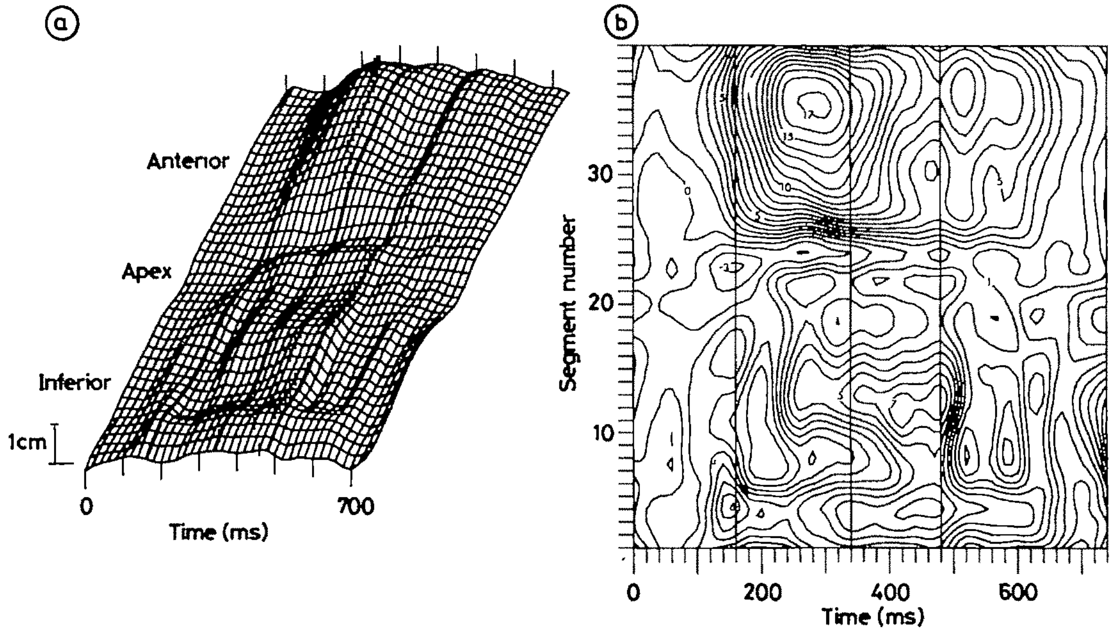

Fig. 2 *(a) Isometric plot of angiogram from a patient with recent right coronary artery thrombosis. Layout as in Fig. 1. There is abnormal outward motion during isovolumic contraction followed by prolonged inward motion along the inferior wall during isovolumic relaxation. On the free wall there is abnormal outward movement during isovolumic relaxation. (b) Contour plot of data from Fig. 2b.*

displays from a normal subject. On the isometric display the horizontal lines represent the 40 original plots of wall movement against time, inward displacement being represented as an upward deviation. The diagonal lines, isochrones, join events occurring simultaneously on the 40 plots. The three accentuated isochrones represent the timing of aortic opening, aortic closure, and mitral opening. The position in the ventricle from which the plots are derived is shown on the left. The contour display is derived from the same information. Each contour represents 1 mm of inward or outward motion of endocardium from its position in the end diastolic frame. The three vertical lines again correspond to aortic opening, aortic closure, and mitral opening. In the normal subject, there is no significant wall motion before aortic valve opening. During ejection, there is synchronous inward movement of endocardium, shown by the contour lines being almost vertical except towards the apex. On the free wall outward motion starts during isovolumic relaxation and precedes that at the apex or on the inferior wall. After mitral valve opening, movement is rapid and synchronous as shown by the closely spaced and vertical contour lines.

## RIGHT CORONARY ARTERY THROMBOSIS

The right coronary artery was occluded by thrombus in eight patients, three of whom had important disease elsewhere (Fig. 2a and b). The general direction of wall motion can be appreciated on the isometric plot (Fig. 2a), and the extent and localisation of any abnormality quantified from the contour display (Fig. 2b). Wall motion is abnormal in all regions of the ventricle. On the inferior wall there is 3 mm outward motion before and immediately after aortic valve opening over segments 5–10. Inward wall motion then occurs, but it is delayed and continues throughout isovolumic relaxation, when 3–4 mm further inward movement is seen along the entire inferior wall. The overall amplitude of inward motion is thus 9–10 mm, well within the 95% confidence limits of normal, although only 4 mm of this occurs during ejection. At the apex, there is akinesis (segments 22–25). Overall amplitude of motion is normal along the free wall, but inward motion starts before aortic valve opening (5 mm in segments 33–40). In addition, during isovolumic relaxation there is 10 mm outward motion from segments 27–35.

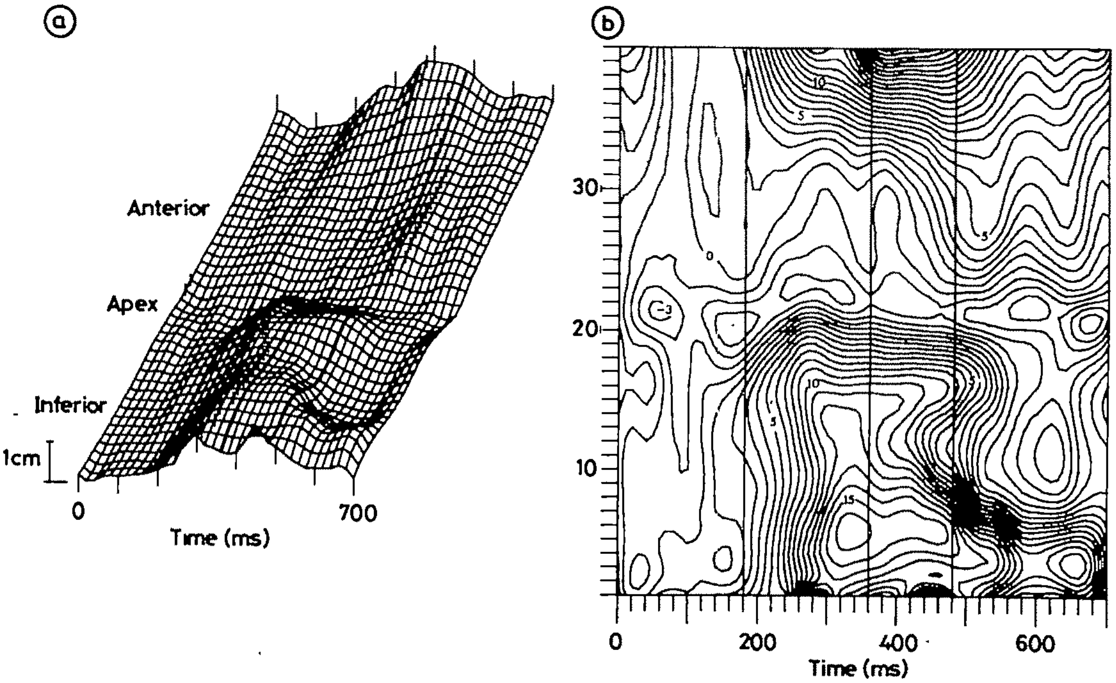

Fig. 3 *(a) Isometric plot of angiogram from a patient with recent anterior descending thrombosis. Movement on the inferior wall is normal, but on the free wall there is dyskinesis during the first half of ejection followed by delayed inward motion of 5 mm reaching a peak at the time of mitral opening. (b) Contour plot of data from Fig. 3a.*

In the group as a whole, the inferior wall was hypokinetic in only two, one of whom had an ejection fraction of 33%, while in the remainder the overall amplitude of inferior wall motion was within normal limits. Dyskinesis was not seen in any patient with right coronary artery thrombosis. On the free wall the amplitude of wall motion was increased in two patients to 23 and 24 mm (both in group 1) and was normal in the remainder. During ejection values were low (between 2 and 4 mm on the inferior wall in seven patients) and segments 10 (2) to 17 (3) (mean (1 SD)) were affected in group 1 and 5 (1) to 13 (3) in group 2. The difference between the overall amplitude of motion and that during ejection reflected abnormal movement during the two isovolumic periods. In six out of the eight patients this occurred during isovolumic contraction and early ejection and affected segments 9 (3) to 15 (3). At the same time, early inward movement of endocardium of 4–8 mm occurred in six patients in the anterior region of the cavity before aortic valve opening, confirming that cavity shape was changing during isovolumic contraction. Wall movement during isovolumic relaxation was also disturbed, with abnormal inward motion of 2 to 4 mm in segments 8 (3) to 12 (2) being recorded in seven of the eight patients. At the same time, abnormal outward movement of 9–13 mm occurred along the free wall in three patients followed by abnormal inward movement during filling in one. Filling was incoordinate, with the timing of peak rate of outward motion showing a mean spread of 105 (70) ms between segments (normal 40 (20) ms), though that of the end of filling (45 (30) ms) was not significantly different from normal (43 (20)). Peak rate of outward motion along the free wall frequently occurred before mitral valve opening (mean 10 (70) ms), while that at the apex followed it by 35 (50) ms and on the inferior wall by 105 (70) ms. The corresponding figures for normal are 40 (30), 40 (30), and 40 (25) ms after mitral valve opening for the anterior, apical, and inferior regions respectively.

### ANTERIOR DESCENDING CORONARY ARTERY THROMBOSIS

The pattern of free wall motion after thrombosis of the anterior descending coronary artery was similar but not identical to that on the inferior wall after thrombosis of the right coronary artery (Fig. 3a and b). Here wall motion is very abnormal, particularly between segments 24 and 33 where there is 2 mm dyskinesis during ejection. This is followed by inward movement, starting late in ejection and continuing throughout isovolumic relaxation to reach a maximum at the time of mitral valve opening. Normal outward movement is seen during filling. The overall amplitude of inward movement is 7 mm, well

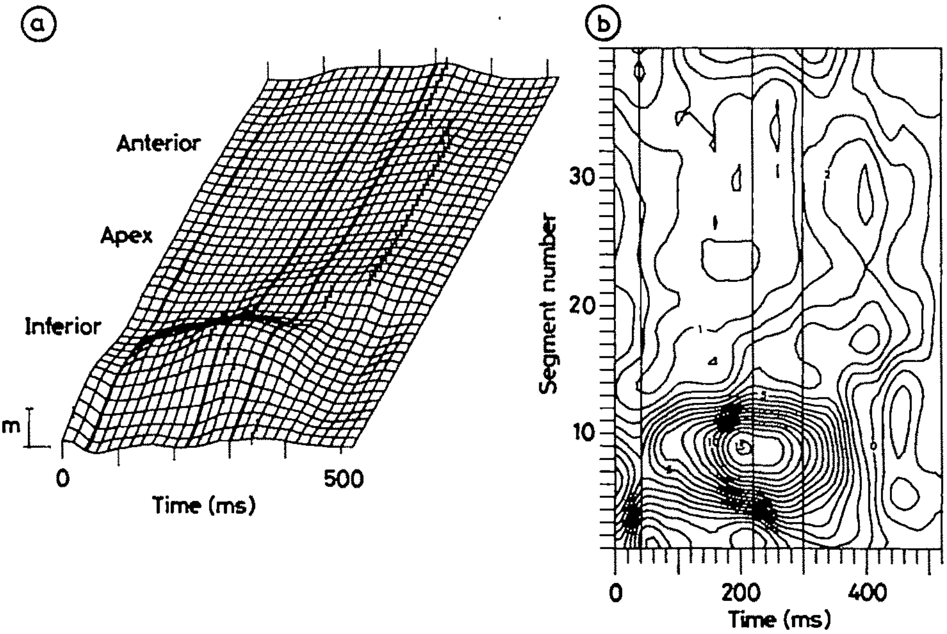

Fig. 4 *(a) Isometric plot of angiogram from a patient with chronic anterior descending and circumflex disease but without evidence of thrombosis. Inferior wall motion is normal but apex and free wall are akinetic. There is no evidence of residual contractile activity. (b) Contour plot of data from Fig. 4a.*

within the normal range for this region. Wall motion in the inferior part of the cavity is normal, both with respect to amplitude and to its time relations, and rapid outward motion of endocardium during ventricular filling is preserved. Thrombosis of the anterior descending coronary artery was seen in seven patients, four of whom had important disease of the other coronary arteries. A reduction in the overall amplitude of systolic wall motion was present at the apex in four patients and also affected the free wall in three. Important hypokinesis was seen during ejection in all. It was maximum along the anterior free wall and at the apex from segments 15 (2) to 25 (3). Its distribution was unaffected by the presence or absence of disease of the other coronary arteries. Dyskinesis of 2 to 5 mm was seen in two patients, involving segments 22–29 and 25–29, that caused an increase to 110 (50) ms in the time interval over which peak rate of inward movement occurred ($p < 0{\cdot}01$, compared with normal). An increase in the amplitude of inferior wall motion to 19 mm was seen in one patient. As after right coronary occlusion, the time relations of this hyperkinetic motion were normal. During isovolumic contraction there was no evidence of the early outward motion of endocardium on the free wall resembling that seen along the inferior wall after right coronary artery occlusion. During isovolumic relaxation, however, inward motion of 3–5 mm was seen in each of the three patients with isolated anterior descending coronary artery disease (segments 23–35, 23–31, and 22–30) and in one of five in group 2. During filling, outward wall motion was not incoordinate, as it was in patients with inferior infarction; the normal pattern was preserved with peak outward movement following mitral valve opening at all three sites. The spread of the timing of both the peak and the end of rapid outward motion between regions was also normal.

### CIRCUMFLEX CORONARY ARTERY THROMBOSIS

The disturbance to wall motion after circumflex occlusion closely resembled that after occlusion of the right coronary artery. Overall amplitude of inferior wall motion was low in one of the four patients. During ejection it was reduced in all to 2–4 mm, over segments 8 (3) to 15 (2). Dyskinesis was not seen. In two patients there was synchronous hyperkinesis of the anterior wall (19 mm and 21 mm). Abnormal outward movement of 3 mm during isovolumic contraction was present in two patients in segments 14–18 and 17–20, and there was abnormal inward movement of the free wall of 6 mm in one. In three patients there was prolonged inward motion during isovolumic relaxation of 3–6 along the inferior wall; one of them also showed 16 mm early outward movement on the anterior wall. The spread in the timing of the peak and end of rapid filling were 70 (75) ms, and 120 (50) ms respectively, considerably greater than normal, although the difference was not statistically significant at a sample size of four. No difference in the pattern of wall movement was present between the patients in group 1 and those in group 2.

### PATIENTS WITHOUT DEMONSTRABLE THROMBOSIS

These patients demonstrated various disturbances of wall motion. All the four patients with important disease of the left anterior descending coronary artery had hypokinesis affecting the free wall, and in one there was dyskinesis of 2 mm affecting segments 22–26. An example is given in Fig. 4a and b. Here, there is a very extensive area of akinesis covering segments 14–40. Wall motion along the inferior wall is normal, both with respect to amplitude and also timing, with no disturbance during isovolumic contraction or relaxation. There is no disturbance of wall motion over the remainder of the ventricle.

Only one patient (with left main stem disease) showed early outward movement of endocardium at the apex (18–22), and none had any abnormality of wall motion during isovolumic relaxation. A patient with anterior descending coronary artery disease showed an increase in the amplitude of inferior wall motion to 22 mm, while in the remainder it was normal.

## Discussion

Impairment of left ventricular function is a major cause of disability and death after acute coronary occlusion, and early and late mortality can be shown to be closely related to the extent of infarcted myocardium.[9 10] The advent of procedures for revascularisation has altered the natural history of coronary thrombosis, so that the development of myocardial infarction in the absence of an adequate collateral flow is no longer inevitable. It seems reasonable to postulate a phase of partial loss before irreversible loss of function occurs. This might be termed impending myocardial infarction. Although there is no definite evidence for its existence in man, it might be recognisable from a pattern of wall motion intermediate between normal and one that is wholly passive. Experimental studies suggest that the main characteristics of such wall motion might be a reduction in peak force and prolongation of tension development, with significant myocardial shortening occurring only as ventricular pressure falls at the end of ejection.[11] Contrast angiography is a particularly suitable method for studying regional wall motion in man. Its resolution in space is considerably superior to that of cross sectional echocardiography or radionuclide angiography, and frame rates of 50/s are readily attained. Because it is an invasive technique its use is necessarily limited, but when records are already being obtained as part of the clinical management of patients it seems desirable to extract the maximum information from them. We digitised all the frames in each cardiac cycle in order to study asynchronous wall motion rather than only those at end diastole and end systole, as in previous studies in which wall motion was analysed after acute myocardial infarction.[12 13] This proved to be essential if partial loss of function was to be detected. It also allowed us to avoid errors in the quantification of regional wall motion associated with use of only two frames.[14]

Although all the patients studied had evidence of impending myocardial infarction, overall measures of left ventricular function were usually normal. This applied not only to ventricular volumes and ejection fraction, but also to peak ejection and filling rates. For all these quantities, estimates outside the 95% confidence limits of normal were seen in only a few cases, and it was striking that all could be within normal limits in patients with severe disturbances of regional motion. Our observations thus extend those of Sheehan *et al*[15] in demonstrating the relative insensitivity of these overall measurements of left ventricular function in detecting the effects of impending myocardial infarction.

The original experiments of Tennant and Wiggers in animals showed that regional akinesis or dyskinesis was a specific feature of acute coronary artery occlusion.[16] Similar findings have been demonstrated by cross sectional echocardiography after acute myocardial infarction in man.[17-19] These studies were based on subjective examination of video tapes; normal limits for regional wall motion were not defined nor was the possibility of asynchrony considered. Regional hypokinesis has also been demonstrated angiographically by shortening of hemicords,[20] subjective wall motion scores,[21] reduction in regional ejection fraction,[22] or use of multiple plots derived by the "center line" technique.[23] Unlike these previous studies, we found the incidence of overall hypokinesis to be low in regions supplied by occluded coronary arteries. In part this arose from our use of 95% confidence limits. These are wide, making the definition of hypokinesis a strict one. The main reason, however, for the discrepancy was that appreciable wall motion also occurred during the two isovolumic periods, so that the inward component during ejection was reduced despite the overall amplitude being within normal limits. The distribution of hypokinesis during ejection corresponded closely with that of the affected artery as demonstrated by the right anterior oblique projection. Dyskinesis was less common and occurred in only three patients all of whom had occlusion of the anterior descending coronary artery.

Asynchrony was the most common disturbance of wall motion in the first few hours after coronary occlusion. Several manifestations could be recognised. In the territory of the occluded coronary artery the commonest disturbance was considerable inward motion of endocardium during isovolumic relaxation instead of the slight outward motion usually seen in normal individuals. This inward motion reached its peak at the time of mitral valve opening. When the thrombus affected the right or circumflex coronary artery we also noted abnormal outward endocardial motion of 2 mm or more along the inferior wall during isovolumic contraction and early ejection followed by inward motion later in ejection, which usually continued until aortic valve closure to merge with inward motion during isovolumic relaxation. Associated with these disturbances in the region supplied by the occluded coronary artery, distant abnormalities were also seen, again in the two isovolumic periods. Early outward motion of the inferior wall during isovolumic contraction was associated with abnormal inward movement of the free wall before aortic valve opening. Similarly, prolonged inward motion during isovolumic relaxation of the inferior wall was associated with early outward motion of the free wall, often amounting to 10 mm or more by the time of mitral valve opening, previously referred to as SERP (segmental early relaxation phenomenon.[24] Both these latter disturbances appear to be manifestations of an overall change in cavity shape at a time of constant cardiac volume and so result directly from changes in the ischaemic area. It is not necessary to postulate any additional mechanism such as ischaemia at a distance from the original infarct to explain them.

Detailed analysis of these abnormalities of wall motion demonstrated important differences in pattern depending on the position of the affected myocardium within the ventricle. Thus, outward motion during isovolumic contraction did not occur on the free wall after thrombosis of the anterior descending coronary artery as it did on the inferior wall after that of the right or circumflex. True dyskinesis, that is outward motion of endocardium throughout ejection, was seen only on the anterior wall and not along the inferior wall in any of the eight cases with right coronary artery occlusion. In addition, delayed inward movement during isovolumic relaxation occurred on the inferior wall after right coronary artery occlusion whether or not other coronary arteries were affected; while on the anterior wall it was seen only with isolated left coronary artery occlusion and not when other vessels were affected. Finally, outward motion of endocardium during isovolumic contraction occurred almost exclusively on the free wall after right or circumflex coronary thrombosis but not on the inferior wall after occlusion of the anterior descending coronary artery. Dependence of the pattern of wall motion on the region of the ventricle affected as well as on the coronary arteries affected also occurs in patients with chronic coronary artery disease so the precedent for variation of this sort is clearly established.[25]

These complex abnormalities in the timing of wall motion cannot be explained on the basis of simple movement of the heart in space. The possibility arises that they might be due to tethering,[26] implying that affected myocardium shows no appreciable intrinsic contractile activity and that any motion is passive and due to the physical proximity of a normally functioning region. This mechanism is incompatible with the unique phase relations of the affected areas, which differ both from normal and akinetic myocardium. If myocardium in affected areas behaved in a purely passive manner it would move outwards with systolic tension development and inwards again with the onset of diastole. Although outward motion did indeed occur during isovolumic contraction and early ejection as would be expected from simple passive behaviour, inward motion during late ejection before aortic valve closure is incompatible with this mechanism. Similarly, inward motion of these areas continued only during isovolumic relaxation, and was reversed during rapid filling at a time when ventricular pressure continued to fall, again a feature incompatible with purely passive behaviour. The likeliest explanation seems to be that residual contractile activity persists in these affected regions. In most instances such areas showed delayed inward wall motion during isovolumic relaxation, when ventricular pressure is likely to have been falling and the wall stress was thus lower than that during ejection. Such delayed and reduced contraction has been observed experimentally with hypoxia[11] and after reperfusion.[27 28] The pattern of regional wall motion thus suggests that the functional disturbance caused by coronary thrombosis in man may differ from that due to acute occlusion in animal models, and that it is incompatible with that predicted on the basis of purely passive behaviour. This is probably because coronary artery thrombosis usually occurs in the setting of coronary artery disease, with affected arteries being the seat of pre-existing stenosis. Adaptive changes in the distal vascular bed can thus be postulated, in particular the development of collateral flow. Whatever the mechanism, it seems that in most cases presenting within six hours of the onset of the clinical syndrome of impending myocardial infarction a pattern of wall motion compatible with the persistence of some contractile activity can still be demonstrated in the territory of the affected artery, a finding that may well have clinical relevance when the feasibility of limiting the extent of ischaemic damage is considered.

These results may be of clinical value in assessing the effects of thrombolysis or other procedures designed to increase coronary flow immediately after acute coronary occlusion. They strongly suggest that using ejection fraction or other indices of overall left ventricular function is likely to prove unfruitful, since these measurements are so often normal in the control state. Regional wall motion must thus be studied, but to confine observations simply to its amplitude between frames arbitrarily defined as end diastolic and end systolic is likely to prove misleading. Its timing must also be documented. This not only allows errors associated with the two frame technique to be avoided, but also makes it possible to locate and quantify regions whose behaviour strongly suggests impairment but not loss of contractile activity. This information is potentially available non-invasively in man, for example from cross sectional echocardiography using appropriate methods of analysis and display,[29 30] or from digital subtraction angiography. This might allow the process of patient selection for treatment designed to limit damage caused by infarction to be refined, and also might aid in the assessment of recently introduced procedures such as intravenous thrombolysis.

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# Method of assessing the reproducibility of blood flow measurement: factors influencing the performance of thermodilution cardiac output computers

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SUMMARY Measurements of blood flow by three different makes of thermodilution cardiac output computer in an artificial circulation were analysed by linear regression against absolute flow measured by timed blood volume collection. For each computer the horizontal distance between the 95% confidence limits for a single prediction was calculated at a standard flow rate of 5 litres per minute. This measurement represents the range of flow rates that could give rise to an identical measurement and provides a summary of the reproducibility of the computer's results and its ability to detect a change of flow rate.

This measurement was used to evaluate the effect on each computer's performance of pulsatile or continuous flow, injectate volume, and injectate temperature. With continuous flow the optimum results were 1·8, 0·85, and 0·85 litres per minute and with pulsatile flow they were 1·3, 1·05, and 1·65 litres per minute. There was generally a deterioration in performance when pulsatile flow was evaluated. Under the conditions of the experiment optimum performance in both flow modes was obtained with 5 ml of ice cold injectate, but these findings cannot necessarily be extrapolated to the clinical situation.

With pulsatile flow the overall range of blood flows that could give rise to identical measurements were for each computer 2·0, 1·5, and 3·1 litres per minute, corresponding to 40, 30, and 62% changes of the standard flow rate of 5 litres per minute.

There is no method of determining cardiac output directly. Thermodilution is the most widely used of the indirect and invasive methods of measuring cardiac output based on the Fick principle. There are varying estimates of the reproducibility of thermodilution and conflicting reports on the factors that influence it.[1] We have therefore assessed the accuracy and reproducibility of thermodilution in an artificial circulation using absolute flow rates measured by timed blood volume collection as the reference standard.

Measurements were made by three cardiac output computers simultaneously, with continuous or pulsatile flow at several flow rates, and with various volumes of ice cold or room temperature injectate. For each cardiac output computer measurements of blood flow were correlated with absolute flow rate. The resulting regression equations were used to predict the measurements and their 95% confidence limits that would have been expected at a standard flow rate of 5 litres per minute. The reduction of flow rate necessary for a single measurement to fall outside these confidence limits with 95% certainty was then calculated. This figure was used to summarise the reproducibility of the measurement and the computer's ability to detect a change of flow rate, since in clinical practice the ability to recognise a change of cardiac output is as important as measurement of its absolute value.

## Methods

### ARTIFICIAL CIRCULATION

Figure 1 shows the components of the artificial cir-

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Accepted for publication 17 September 1985

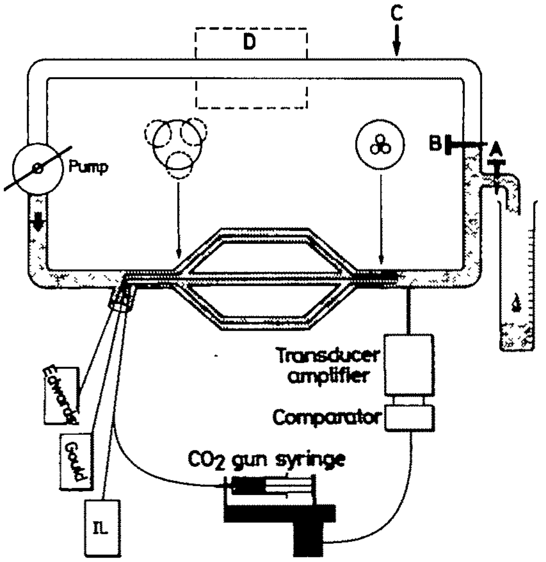

Fig. 1 *Design of artificial circulation. A and B are taps.*

culation which are connected by polyvinyl chloride tubing. A Sands 7400 pulsatile/constant flow pump was provided at "D" and a Cobe Optiflow II bubble oxygenator and heat exchanger connected to a Radiometer Type VTS 13 water heater maintained circulating blood temperature between 36°C and 37·5°C. The system was filled with eight bags of packed red cells (200 ml per bag), polygeline (Haemaccel) 2000 ml, normal saline 800 ml, and silicone antifoam powder to give a circulating fluid volume of 4·4 litres from which all air bubbles were removed. The pump output passed a side arm through which three thermodilution catheters entered, their proximal ports lay 4 cm upstream of a trifurcation of the circulation, each channel contained a thermodilution catheter and carried a third of the total flow for a distance of 6 cm before being reunited 14 cm proximally to the thermistors in the catheter ends. This configuration was adapted from that of Bilfinger *et al*[2] and was designed to avoid a stagnant pool and provide optimal mixing of the indicator by disturbing laminar flow, and also to allow the flow rate to be measured by all three thermodilution computers simultaneously. The distal ends of the thermodilution catheters were fixed in the centre of the flow with their respective thermistors facing outwards; the diameter (1·25 cm) and length of tubing at this point ensured laminar flow at the flow rates being used.

## THERMODILUTION

Table 1 lists the thermodilution cardiac output computers and the catheters with which they were used. All three computers provide a digital read out of "cardiac output" based on automatic computation of the area under the temperature-time curves; Table 1 also indicates the different methods of calculating this area. In the Instrumentation Laboratories computer the curve is displayed on a monitor; in the artificial circulation the curve invariably had a satisfactory appearance and was not recorded.

The injectate was 5% dextrose solution, and when it was used at room termperature it had been stored in the room for at least 16 hours. Ice cold injectate was taken from a 500 ml bottle of 5% dextrose that had been kept in an ice bucket for at least four hours and was drawn into syringes that had been kept in ice for at least 30 minutes. The loaded and capped syringes were then stored in ice for at least 30 minutes before use and injected within five seconds of removal from ice. Injectate volumes of 3, 5, and 10 ml were used with all thermodilution computers, but no results for 3 ml injectate are given for the Instrumentation Laboratories computer since it is not designed to operate at this volume when a 7F catheter is used. The Gould computer gave frequent "out of range" reports with 5 ml injectate at high flow rates.

All injections were made with a carbon dioxide powered syringe driver (OMP Thermodilution Injector, Model 372000). During pulsatile flow the pressure waveform was monitored by an electromagnetic transducer (Druck, model PDCR75), amplified (DC amplifier Roch 1-222), and the signal was used to trigger the syringe injector at the same point in the pump cycle for each measurement.

The injectate temperature was measured by an in-

Table 1 *Thermodilution cardiac output computers, thermodilution catheters, and computation method*

| *Cardiac output computer* | *Thermodilution catheter* | *Cardiac output computation* |
|---|---|---|
| Instrumentation Laboratories IL701 | IL 7F with in-line temperature probe | Area under curve until return to baseline temperature |
| Edwards 9520A | Swan-Ganz 93A-131-7F | Area under curve to 30% of peak temperature change × 1·22 for tail |
| Gould SP1435 with SP2009B printer/recorder | Gould 7F with in-line temperature probe | Area under curve to 87·5% of peak temperature change + area under downslope from 87·5–31·25% peak + 55·55% of preceding area |

line temperature probe on the Instrumentation Laboratories and Gould computers. For the Edwards computer the temperature of the water bath containing the loaded injectate syringe was measured directly.

Measurements were made simultaneously on all three cardiac output computers at several flow rates after injection of 3, 5, and 10 ml volumes of ice cold and room temperature dextrose solution.

### ABSOLUTE FLOW MEASUREMENT

To measure absolute flow rate, tap "A" was opened, tap "B" was closed (Fig. 1), and the time taken to fill a measuring jar was noted with a stop watch; an average of 4·4 measurements was made at each flow rate. The mean coefficient of variation was 0·8% for continuous flow measurements and 2·6% for pulsatile flow.

### STATISTICAL METHODS

For each computer the mode of blood flow, injectate temperature, and injectate volume were analysed by linear regression of computer measurement against absolute flow rate. The predicted measurement ŷ ± standard error of prediction at a standard flow rate of 5 litres per minute was obtained by substitution in the regression equation.[3] The graphical results show the regression line together with 95% confidence limits for a single prediction. The horizontal distance, delta, between the confidence limits at a flow rate of 5 litres per minute was calculated and gave a reduction of flow needed for a single measurement at the new flow rate to fall with 95% certainty outside the confidence limits for measurements at a flow rate of 5 litres per minute. Alternatively delta may be considered as the range of flow rates that could give rise to identical measurements ($p > 0{\cdot}05$). Delta may also be expressed as a percentage of the standard flow rate (D%).

## Results

### THERMODILUTION

Figures 2–5 show the average estimates of blood flow at different flow rates in three different makes of thermodilution machine and at three different injectate volumes. In Figs. 2 and 3 flow is continuous, and in Figs. 4 and 5 flow is pulsatile. Table 2 gives the regression equations derived from these results together with measurements predicted at a standard flow rate of 5 litres per minute.

### EFFECT OF INJECTATE VOLUME

With continuous flow and injectate at room temperature, 10 ml injectate resulted in a larger error of prediction than one of 3 ml or 5 ml. The predicted measurement at a flow rate of 5 litres per minute was also larger in each case at 10 ml, resulting in improved accuracy with the Edwards computer which underestimated the measurements and reduced accuracy with the IL and Gould computers which overestimated the measurements.

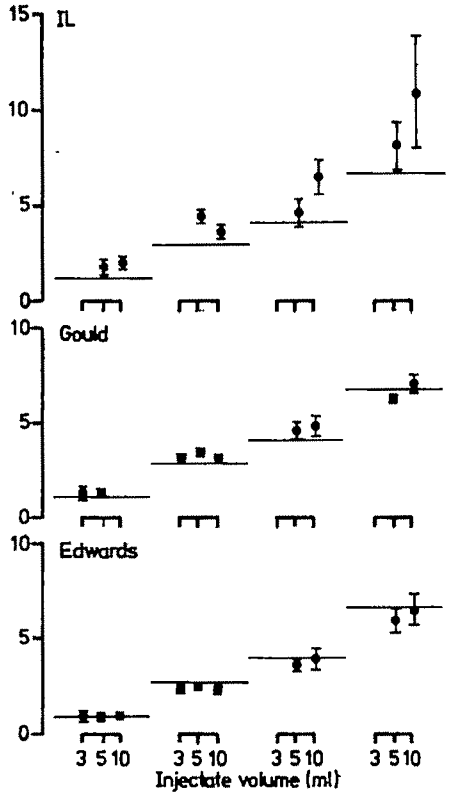

Fig. 2 *Mean ±1 standard deviation of blood flow measurement by three different thermodilution cardiac output computers at various absolute flow rates and various injectate volumes. Value of absolute flow rates is indicated by horizontal lines. Continuous flow, injectate at room temperature.*

With pulsatile flow and injectate at ice temperature, a 5 ml injectate gave least variability with Gould and IL computers but a 10 ml injectate gave least variability with the Edwards computer; there was no consistent effect on accuracy. With continuous flow and ice cold injectate and with pulsatile flow and room temperature injectate there was no consistent effect on either accuracy or variability.

### EFFECT OF PULSATILE FLOW

Pulsatile flow produced a pronounced increase in the variability of measurements, with the standard error of the prediction being approximately double that with continuous flow in most cases. The accuracy of

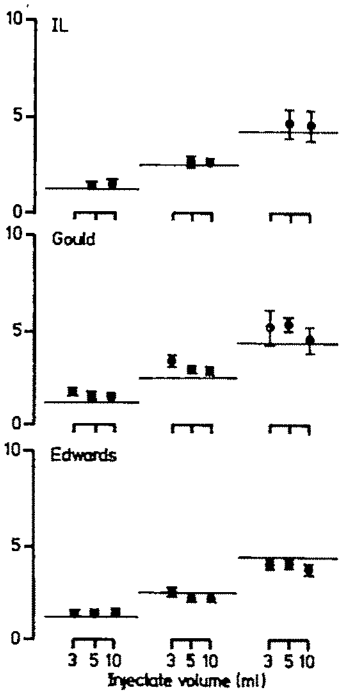

Fig. 3 *As in Fig. 2 but with ice cold injectate.*

the measurements was reduced with flow rates being overestimated, sometimes very substantially.

EFFECT OF INJECTATE TEMPERATURE

Use of ice cold injectate instead of injectate at room temperature reduced the variability and improved the accuracy of the IL and Edwards but not the Gould computer during continuous flow measurements. Use of ice cold injectate with pulsatile flow reduced variability but led to a further substantial overestimation of flow rate, except in the case of the IL computer where there was a slight reduction in the gross overestimate present with pulsatile flow.

OPTIMUM AND OVERALL PERFORMANCE

With pulsatile flow the highest correlation coefficient and the lowest percentage horizontal distance between confidence limits (D%) were obtained by each computer with a 5 ml ice cold injectate. Under these conditions the lowest standard error of prediction was 0·48 litres per minute, that is 9·6% of the flow rate of 5 litres per minute used in the prediction. Figures 6 to 8 show the regression lines relating measurements made by the three cardiac output computers to flow rates together with 95% confidence limits for a single prediction when 5 ml of ice cold solution was injected. The 95% confidence limits at a flow rate of 5 litres per minute are ±1·3, ±1·0, and ±1·5 litres per minute, and the percentage horizontal distance between confidence limits (D%) is 26%, 21%, and 33% of the standard flow rate for IL, Gould, and Edwards cardiac output computers respectively.

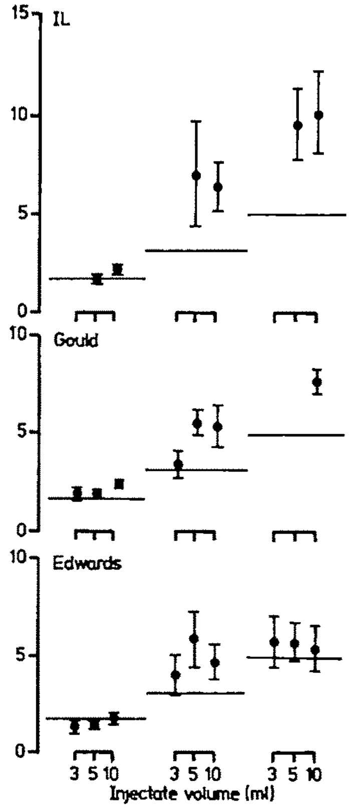

Fig. 4 *As in Fig. 2 but with pulsatile flow, and injectate at room temperature.*

Injectate temperatures and volumes giving the most accurate predictions of pulsatile flow rate were different for each computer. The predictions were 9·47, 5·29, and 5·77 litres per minute for IL, Gould, and Edwards computers and the corresponding percentage horizontal distances between confidence limits were 26, 66, and 87% respectively.

During pulsatile flow with injectate volumes of 5 or 10 ml at room or ice temperature the percentage horizontal distances between confidence limits were 40%, 30%, and 62% for IL, Gould, and Edwards computers. These values summarise each computer's overall performance and correspond to a range of blood flows of 2·0, 1·5, and 3·1 litres per minute which could give rise to identical measurements (Figs. 9–11).

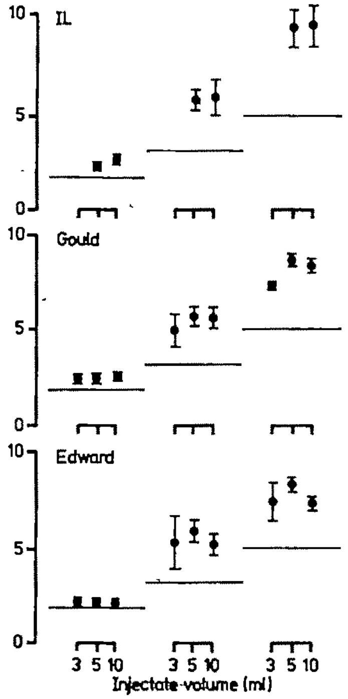

Fig. 5 *As in Fig. 2 but with pulsatile flow, and ice cold injectate.*

### COMPARISONS BETWEEN CARDIAC OUTPUT COMPUTERS

With pulsatile flow all three cardiac output computers overestimated absolute flow rate but when compared with each other accuracy is apparently greatly improved. This suggests that the factors resulting in loss of accuracy with pulsatile flow affect all three computers similarly. Table 3 gives a correlation matrix based upon 63 simultaneous measurements made with ice cold and room temperature injectate of 5 and 10 ml.

## Discussion

### MEASUREMENT OF CARDIAC OUTPUT BY FICK

The direct Fick method is the reference method for measuring cardiac output in man.[4] This technique requires the measurement of partial pressures of oxygen and carbon dioxide in expired air, and measurement of oxygen saturations in arterial and mixed venous blood over several minutes. Important sources of error are incomplete gas collection, inadequate mixed venous sampling, and a non-steady state.[5] Right heart catheterisation is required as well as arterial sampling since the only satisfactory source of mixed venous blood is the pulmonary artery. Unless the patient is intubated a high degree of patient cooperation is required to get a complete gas collection. The quoted error of the method is about 10%,[6] but although the median difference in duplicate readings was 8·6% the results were skewed and 13% of readings had differences greater than 19%.[7]

The Fick principle, with its assumption of steady state conditions, is poorly adapted to measuring pulsatile flow with oxygen as a dilutant; oxygen enters the circulation phasically with respiration. The latter problem is overcome by dye and thermodilution methods in which a known quantity of marker is injected into the circulation. The underlying theory generally assumes continuous flow[8 9] but a mathematical proof of the validity of applying the method to pulsatile flow has been given.[10]

### DYE DILUTION

The direct Fick method for measuring cardiac output was superseded by dye dilution, and while there appear to be no systematic differences between the two techniques, individual differences may be pronounced. Thus 12 of 53 comparisons varied by >25%,[11] six of 48 comparisons differed by >25%,[12] and 26 of 105 comparisons deviated by >20% from the line of identity.[13] The total dose of dye limits the number of measurements that may be made in any individual.

### THERMODILUTION

Thermodilution has now supplanted dye dilution as the standard method of cardiac output measurement.[14] The advantage over dye dilution is that the marker is innocuous so there is virtually no limit to the number of measurements that may be made, and recirculation is not a major problem.[1] Difficulties result from the use of heat as a marker, however, because an unknown quantity of thermal indicator may be lost from the injectate before it enters the circulation,[15] and subsequently from the circulation through the vessel wall.[16] Intrathoracic blood temperature may fluctuate due to a phasic exchange of heat with air in the lungs[17] and a variable return of cooler venous blood from the periphery.[18] The former problem is overcome by the inclusion of a correction factor in the calculation of cardiac output to allow for loss of cold injectate, which can be minimised by using injectate at room temperature.[19] Reducing the temperature differential between blood and injectate, however, increases the effect of "noise" in the baseline temperature measurement on the calculation of the area under the temperature time curve.

When they introduced the technique of thermodilution Ganz *et al* compared it with dye dilution

Table 2 *Correlation coefficients and regression equations relating flow rate and its estimation by three different makes of thermodilution cardiac output computer*

| *Thermodilution computer* | *Injectate volume (ml)* | *r* | *a* | *b* | *SEE* | *ŷ* | *SEP* | *Delta* | *D%* | *n* |
|---|---|---|---|---|---|---|---|---|---|---|
| *Continuous flow—room temperature injectate* | | | | | | | | | | |
| IL | 5 | 0·91 | 0·95 | 0·93 | 0·62 | 5·61 | 0·70 | 3·15 | 63 | 21 |
| | 10 | 0·88 | −0·38 | 1·64 | 1·98 | 7·84 | 2·09 | 5·25 | 105 | 29 |
| Gould | 3 | 0·98 | 0·27 | 1·01 | 0·18 | 5·30 | 0·29 | 1·30 | 26 | 12 |
| | 5 | 0·97 | 0·48 | 0·97 | 0·33 | 5·33 | 0·37 | 1·60 | 32 | 21 |
| | 10 | 0·98 | 0·42 | 0·98 | 0·43 | 5·33 | 0·45 | 1·90 | 38 | 29 |
| Edwards | 3 | 0·97 | 0·24 | 0·78 | 0·16 | 4·14 | 0·25 | 1·40 | 28 | 12 |
| | 5 | 0·99 | 0·25 | 0·85 | 0·22 | 4·49 | 0·24 | 1·20 | 24 | 21 |
| | 10 | 0·96 | −0·04 | 0·98 | 0·59 | 4·88 | 0·63 | 2·65 | 53 | 29 |
| *Continuous flow—ice cold injectate* | | | | | | | | | | |
| IL | 5 | 0·96 | −0·19 | 1·13 | 0·40 | 5·44 | 0·47 | 1·80 | 36 | 19 |
| | 10 | 0·93 | 0·10 | 1·03 | 0·52 | 5·25 | 0·58 | 2·35 | 47 | 24 |
| Gould | 3 | 0·93 | 0·19 | 1·16 | 0·60 | 5·98 | 0·69 | 2·50 | 50 | 21 |
| | 5 | 0·99 | −0·14 | 1·24 | 0·21 | 6·08 | 0·25 | 0·85 | 17 | 19 |
| | 10 | 0·94 | 0·33 | 0·98 | 0·45 | 5·22 | 0·51 | 2·15 | 43 | 24 |
| Edwards | 3 | 0·99 | 0·15 | 0·88 | 0·16 | 4·54 | 0·18 | 0·85 | 17 | 21 |
| | 5 | 0·99 | 0·15 | 0·88 | 0·15 | 4·57 | 0·18 | 0·85 | 17 | 19 |
| | 10 | 0·99 | 0·29 | 0·78 | 0·17 | 4·21 | 0·19 | 1·00 | 20 | 24 |
| *Pulsatile flow—room temperature injectate* | | | | | | | | | | |
| IL | 5 | 0·87 | −3·71 | 2·87 | 1·08 | 10·64 | 1·85 | 2·95 | 59 | 11 |
| | 10 | 0·91 | −1·93 | 2·42 | 1·41 | 10·16 | 1·57 | 2·75 | 55 | 20 |
| Gould | 3 | 0·87 | 0·18 | 1·02 | 0·35 | 5·29 | 0·71 | 3·30 | 66 | 9 |
| | 5 | 0·97 | −2·94 | 2·64 | 0·40 | 10·25 | 0·68 | 1·20 | 24 | 11 |
| | 10 | 0·94 | −0·30 | 1·62 | 0·73 | 7·79 | 0·81 | 2·10 | 42 | 20 |
| Edwards | 3 | 0·87 | −0·76 | 1·36 | 0·94 | 6·03 | 1·06 | 3·30 | 66 | 19 |
| | 5 | 0·91 | −3·80 | 2·81 | 0·86 | 10·25 | 1·48 | 4·80 | 48 | 11 |
| | 10 | 0·81 | 0·58 | 1·04 | 0·96 | 5·77 | 1·07 | 4·35 | 87 | 20 |
| *Pulsatile flow—ice cold injectate* | | | | | | | | | | |
| IL | 5 | 0·98 | −1·62 | 2·22 | 0·58 | 9·47 | 0·66 | 1·30 | 26 | 18 |
| | 10 | 0·92 | −0·73 | 2·05 | 0·87 | 9·51 | 1·01 | 2·15 | 43 | 14 |
| Gould | 3 | 0·92 | −0·39 | 1·59 | 0·63 | 7·53 | 0·73 | 1·95 | 39 | 23 |
| | 5 | 0·99 | −1·10 | 1·96 | 0·42 | 8·70 | 0·48 | 1·05 | 21 | 18 |
| | 10 | 0·97 | 0·06 | 1·63 | 0·44 | 8·22 | 0·51 | 1·35 | 27 | 14 |
| Edwards | 3 | 0·83 | −0·28 | 1·60 | 1·19 | 7·73 | 1·30 | 3·35 | 67 | 28 |
| | 5 | 0·97 | −1·04 | 1·93 | 0·65 | 8·59 | 0·74 | 1·65 | 33 | 18 |
| | 10 | 0·94 | 0·65 | 1·35 | 0·51 | 7·39 | 0·60 | 1·95 | 39 | 14 |

r, correlation coefficient for which the regression equation is $y = a + bx$ where x is flow rate, y is cardiac output computer measurement, SEE, standard error of the estimate, $\hat{y}$ is predicted value of measurement for $x = 5$; SEP, standard error of prediction, delta, horizontal distance between 95% confidence limits at an upper flow rate of 5; D%, delta × 100/5 Units are litres per minute.

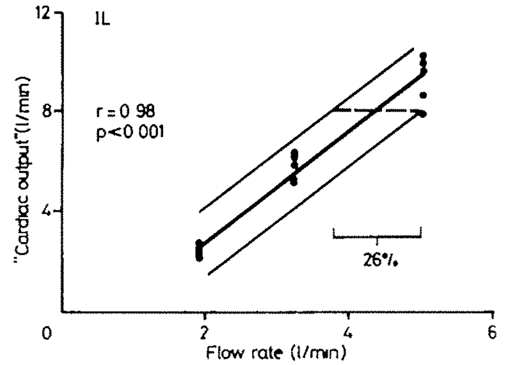

Fig. 6 *Regression of individual measurements of blood flow by IL thermodilution cardiac output computer against absolute blood flow together with 95% confidence limits for a single prediction. Horizontal distance between confidence limits is expressed as a percentage of standard flow rate of 5 litres per minute. Optimal results with 5 ml ice cold injectate. In Figs. 6 to 11 scales for axes differ to accommodate overestimation of flow rate by all three cardiac output computers.*

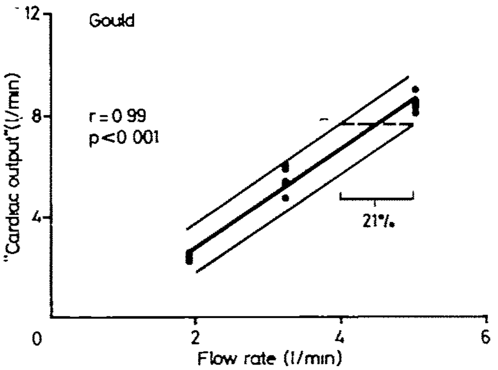

Fig. 7 *As in Fig. 6 but for Gould computer.*

and the correlation coefficient was 0·96 with a standard error of the estimate of 0·36 litres per minute or 7% of the mean cardiac output which was about 5 litres per minute.[20] In clinical studies other groups have obtained coefficients of correlation between thermodilution and dye dilution methods ranging

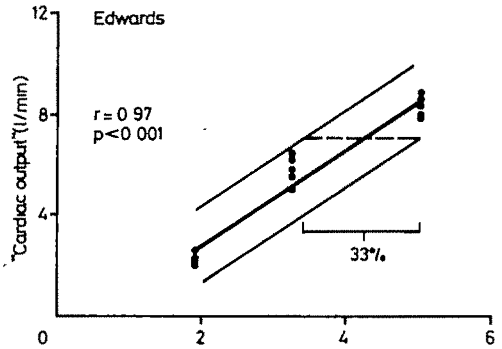

Fig. 8 *As in Fig. 6 but for Edwards computer.*

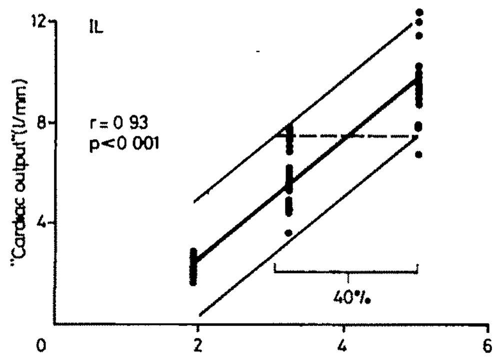

Fig. 9 *As in Fig. 6 but showing overall results for 5 ml and 10 ml of ice cold or room temperature injectates and an IL computer.*

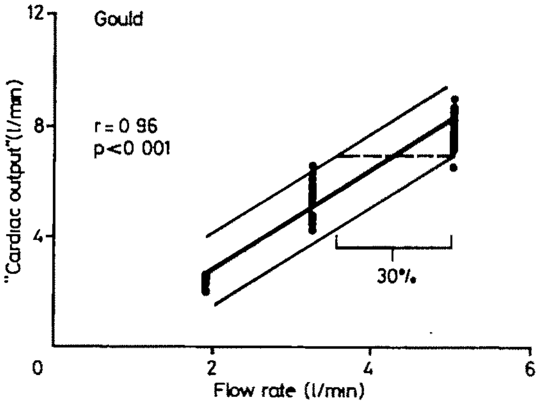

Fig. 10 *As in Fig. 9 but for a Gould computer.*

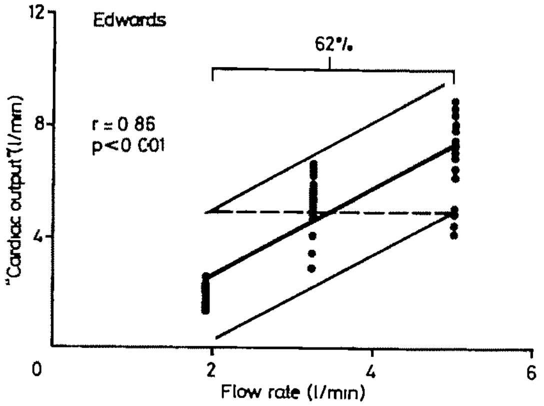

Fig. 11 *As in Fig. 9 but for an Edwards computer.*

from 0·90 to 0·99,$^{21-25}$ and correlation coefficients were 0·70 and 0·93 when the thermodilution method was compared with direct Fick.$^{26\ 27}$

Fischer *et al* used an injectate of cold indocyanine green for simultaneous measurement of cardiac output by thermodilution and dye dilution in cardiothoracic patients in the operating theatre and intensive care unit.$^{28}$ By duplicating all measurements they were able to estimate the proportions of total variance that could be attributed to flow change between measurements, random error, and calibration error of dye and thermodilution sep-

Table 3 *Correlation matrix giving correlation coefficients and prediction of measurement and standard error of prediction based on 63 simultaneous estimates of pulsatile flow rate by three different makes of thermodilution cardiac output computer with ice cold and room temperature injectates of 5 and 10 ml*

| *y*<br>x | *Flow rate* | *IL* | *Gould* | *Edwards* |
|---|---|---|---|---|
| Flow rate | r<br>ŷ (SEP) | 0·933<br>9·80 (1·14) | 0·961<br>8·31 (0·66) | 0·859<br>7·31 (1·17) |
| IL | 0·933<br>3·02 (0·45) | — | 0·961<br>4·65 (0·65) | 0·869<br>4·18 (1·11) |
| Gould | 0·961<br>3·20 (0·34) | 0·961<br>5·52 (0·87) | — | 0·941<br>4·47 (0·76) |
| Edwards | 0·859<br>3·48 (0·64) | 0·869<br>6·22 (1·55) | 0·941<br>5·56 (0·79) | |

r, correlation coefficient for which the regression equation is $y = a + bx$ where x is flow rate, and y is cardiac output computer measurement; $\hat{y}$ is predicted value of measurement for $x = 5$; SEP, standard error of prediction. Units are litres per minute.

arately. In the intensive care unit, where patients were haemodynamically more stable than in the operating theatre, flow change was 5% between measurements, reproducibility was 10% and 11%, and the random error of a single measurement by dye dilution and thermodilution was 5·5% and 6·5% respectively. This study, however, and the others cited, all have the drawback that there is no absolute yardstick of cardiac output measurement, and the comparability of results from two related techniques does not rule out the occurrence of a systematic error that affects both. The correlation between two indicator dilution techniques may be closer than that between thermodilution and the direct Fick method with which thermodilution has less often been compared.

An electromagnetic flowmeter has been used to measure cardiac output in dogs and calves, and the correlation coefficients compared with thermodilution were 0·97 and 0·98, with standard errors of the estimate of 0·45 and 0·75 litres per minute respectively.[29]

## STATISTICAL ASPECTS OF REPRODUCIBILITY

The correlation coefficient is commonly used to express the relation between measurements of cardiac output made by two different methods. Its value is, however, influenced by the range of values studied, so that it may be substantially increased by a single outrider. The standard error of the estimate gives more information about the scatter of values around the regression line, and hence the confidence of a prediction, than the r value. The standard error of the estimate, however, is closely related to the correlation coefficient and has some of its limitations. Unfortunately, in published reports on cardiac output measurement even the standard error of the estimate is not always quoted or there is insufficient raw data to make meaningful comparisons between different reports.

We have used the standard error of the prediction as a means of expressing variability.[3] It increases as the predictor variable moves away from its mean value, and its calculation at a standard flow rate of 5 litres per minute allows direct comparison of variability measured under different experimental conditions. By itself, the standard error of the prediction, or any other measure of variability such as the standard error of the estimate, is insufficient to describe the performance of a method for measuring cardiac output since an instrument which gives the same measurement whatever the flow rate would have low variability but would not fulfil its clinical function of measuring a change of cardiac output.

The standard error of the prediction is approximately one quarter of the vertical distance between 95% confidence limits for a single prediction. The horizontal distance between confidence limits has been used in this paper to provide a summary of the overall performance of the cardiac output computers. It is related to the vertical distance by the slope of the regression line relating measurement and flow rate, thus overcoming the objection to the use of a measure of variability by itself. In the case of an instrument that gives the same result whatever the flow rate its value would be infinitely large. The horizontal distance between confidence limits represents the range of flow rates that could give rise to the same measurement. It is equal in value to the vertical distance between confidence limits if the regression is reversed and flow rate is regressed on its measurement. It is not the same as the minimum change of flow that may be recognised; providing the slope of the regression line is not zero any change of flow rate may be detected if a sufficient number of measurements is made.

## IN VITRO VALIDATION OF THERMODILUTION

Bilfinger *et al* evaluated the performance of an Edwards cardiac output computer in an in vitro model using a continuous flow roller pump.[2] With a 10 ml injectate at room temperature the mean accuracy of estimates of six flow rates was within 7% with a coefficient of variation of 5·4%. Neither the volume or temperature of the injectate had any influence on their results. In our circulation model, adapted from that of these workers, the Edwards computer measured four flow rates with a mean accuracy of 3·2% and a coefficient of variation of 9·6%, the total error with our model under conditions of continuous flow being very similar in magnitude to that of Bilfinger *et al.*

Powner and Snyder compared six thermodilution cardiac output systems in vitro using a pulsatile pumping unit,[30] but none of the models we studied was included. The standard deviations of the measurements at a flow rate of 4·26 litres per minute (the nearest value to our standard flow rate of 5 litres per minute) varied from 0·046 to 0·11 litres per minute with room temperature injectate and 0·052 to 0·19 litres per minute with ice cold injectate. The same pulsatile flow rate was under or overestimated by −8·7 to +9·2% with room temperature injection and −0·2 to +23·5% with iced injectate. Reproducibility and accuracy were generally better than in our circulatory model but no clear relation with our own results emerges, and the most important conclusion may be that the operating conditions for optimal reproducibilty or accuracy in one experiment may not be the same as in another. By

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implication, the results in our artificial circulation may not be applicable to the clinical situation.

### INJECTATE TEMPERATURE

Shellock *et al* compared thermodilution cardiac output measurements using ice cold and room temperature injectates and concluded that the measurements and their variability were similar by both methods, both in critically ill subjects with a normal body temperature[31] and in hypothermic surgical patients.[32] Other groups have shown that the use of room temperature rather than ice cold injectate increased the variability of the results, but the increase in the coefficient of variation has not always been statistically significant.[33 34]

Our experiments showed that the use of ice cold injectate generally reduced the variability of measurements compared with that when the injectate was at room temperature, as would be expected theoretically. With continuous flow and ice cold injectate, the pooled measurement prediction at a flow rate of 5 litres per minute was overestimate by only 2·2%, indicating that the correction factors for loss of marker from the injectate are more or less correct in our experimental model.

### EFFECT OF PULSATILE FLOW

With continuous flow, the temperature-time curve declines exponentially after the maximum temperature difference has been reached, enabling the time at which temperature returns to the baseline value to be predicted from the slope of the earlier part of the curve. This may be advantageous since otherwise the correct calculation of the area of the tail of the curve is critically dependent on absence of fluctuation of baseline temperature. Since the estimation of the total area under the curve, and hence cardiac output per minute, is based on a time sample considerably shorter than a minute, the shorter the time-base of the calculation the larger the sampling error. This is of little moment if flow is continuous, but is potentially an important source of error when flow is discontinuous or pulsatile.

Pulsatile flow brings an additional problem: the concentration-time curve for the marker no longer shows a smooth exponential decline but is stepped in phase with systole. The damping of the response produced by use of a cuvette in dye dilution has the effect of smoothing the exponential curve, and this may be achieved electronically in the design of the thermistors used in thermodilution. Although theoretically a slightly delayed response of the marker detecting system should not alter the area under the curve,[10] it has been found that use of a thermistor with a long time constant reduces the area and overestimates the flow rate.[35] On the other hand, if the curve is inadequately smoothed, estimation of the mean rate of exponential decline is subject to considerable error.

The mathematical validity of thermodilution as a method of calculating cardiac output when flow is pulsatile depends on absence of overlap between the frequency spectra of flow (determined principally by the heart rate) and the process of mixing and thermodilution.[36] Theoretically, the error due to pulsatility is small, but theory indicates a particular susceptibility to low frequency fluctuations in flow rate, such as are associated with respiration, and this has been found in practice.[37]

Our circulation model permits comparison between measurements of continuous and pulsatile flow. The roller pump we used closely simulates naturally occurring pulsatile flow, as judged by the similar appearances of the Doppler ultrasound recordings in vitro and in vivo.[38] In all three cardiac output computers accuracy and variability were significantly worse with pulsatile than with continuous flow. The pooled result of the predicted measurement at a continuous flow rate of 5 litres per minute was 5·6 (1·1) litres per minute and that during pulsatile flow was 8·1 (1·2) litres per minute. The explanation for this overestimation during pulsatile flow is unlikely to be a greater loss of indicator from the circulation since any temperature differential within and without the circulation is unlikely to be altered by the pattern of flow within it. Pulsatile flow might increase the degree of mixing of the indicator, but this would only cause an increase in the estimation of pulsatile relative to continuous flow if mixing with continuous flow was inadequate. This seems unlikely since with continuous flow both reproducibility and accuracy were better than with pulsatile flow. Error in the calculation of the area under the temperature-time curve is almost certainly the main source of inaccuracy with pulsatile flow. A slow thermistor response may contribute to this inaccuracy, and sampling error is another possible factor.

With pulsatile flow, correct estimation of flow per minute is only possible if the indicator dilution curve that comprises the time sample is equivalent to a whole number of pump cycles. If the time sample always starts with systole or a period of rapid flow and is not an exact number of pump cycles then average flow will be overestimated. Conversely, if the time sample starts with diastole or a period of stationary flow then average flow will be underestimated except when the time sample is an exact number of pump cycles. In our circulation model operation of the injectate pump was synchronised with the pressure wave in all measurements with pulsatile flow in order to minimise variability, but unwittingly reproduced the situation in which overestimation of average flow is probable. If synchronisation has contributed to overestimation of flow rate, then injection of indicator randomly at any phase of the cardiac cycle, which is the case in clinical practice, will result in a substantial increase in variability though this will be accompanied by an improvement in accuracy.

The measurement of cardiac output by thermodilution is influenced by the low frequency fluctuation in flow rate caused by respiration, and it has been suggested that injection of the cold charge should be repeated at intervals throughout the respiratory cycle since the phase relation between ventilation and flow rate is inconstant.[37] The potential for variation of the measurement as cardiac and respiratory cycles interact is considerable.

### INJECTATE VOLUME

Bilfinger *et al* claimed that in vitro neither the temperature nor volume of injectate had any effect on the results from an Edwards cardiac output computer,[2] but using a computer of different make Elkayam *et al* showed that a 10 ml injectate resulted in less variability than either a 5 ml or 3 ml one.[34]

The volume of injectate used in thermodilution is a compromise. At one extreme a small volume leads to a temperature change that is lost in the fluctuation of baseline temperature. At the other extreme a large injectate volume will alter the flow rate (measurement of which is being attempted), will be incompletely mixed with blood flow, and will take an appreciable time to inject in relation to the mean transit time of blood from injection site to sensor. The net effect of increasing injectate volume on the accuracy and variability of thermodilution measurement is unpredictable and in our experiments it was different for each cardiac output computer. Because injectates of different volumes take different times to inject, the volume of injectate may alter the shape and duration of the temperature-time curve and hence alter the sample time, and this may explain why injectate volume has a much greater effect on accuracy during pulsatile than during continuous flow.

### COMPUTATION OF AREA UNDER CURVE

If the main source of error during pulsatile flow results from inaccuracies in computing the area under the temperature-time curve, then computers using similar methods of doing this are likely to give results more closely correlated with each other than with absolute flow or with a computer using a different method of calculating the area under the curve. Thus, the correlation between IL and Gould computers, which use the longest time samples, is closer than the correlation of either with the Edwards computer which uses the shortest sampling time. Many of the errors in the indicator dilution method of determining cardiac output are common to both dye dilution and thermodilution. Comparison of thermodilution and dye dilution does not therefore constitute an adequate validation of either method.

### CONCLUSIONS

Although it may be valid theoretically, thermodilution as a method of measuring cardiac output is riddled with compromises when flow is pulsatile. The injectate volume and temperature for optimum accuracy is different from that for optimum reproducibility, differs from computer to computer, and alters in different experimental or clinical situations.

Thermodilution has usually been validated against another indicator dilution technique which will be similarly susceptible to errors. Our experiments have shown that with pulsatile flow very little reliance can be placed on the absolute measurement of blood flow by thermodilution, and in two out of the three cardiac output computers tested there is a closer correlation with another computer than with absolute flow rate. Under optimum conditions in vitro the standard error of the prediction for a flow rate of 5 litres per minute is seldom less than 0·5 litres per minute or 10%. Under clinical conditions and with the influence of respiration the error of the method is likely to be substantially in excess of this figure. Levitt and Replogle conclude that the overall biological error of any method of cardiac output measurement is 15–20%, and thermodilution falls within that range.[1] Thus, as a gold standard for comparison with newer methods of measuring cardiac output, thermodilution looks somewhat tarnished.[39]

We are grateful to Grampian Health Board for a research grant.

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# Reproducibility of linear cardiac output measurement by Doppler ultrasound alone

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SUMMARY Inclusion of a pig aorta in an artificial circulation with pulsed blood flow allowed correlation of minute distance, measured in the aorta by Doppler ultrasound, and absolute blood flow, measured by timed blood-volume collection. The correlation coefficient was 0·99 with a standard error of prediction that was 5·4% of the minute distance predicted at a standard flow rate of 5 litres per minute. The horizontal distance between 95% confidence limits for a single prediction expressed as a percentage of 5 litres per minute was 33%, and this corresponded to the range of flow rates of 1·65 litres per minute that could give rise to the same measurement.

In 142 patients duplicate measurements of minute distance were made with repositioning of the ultrasound transducer between recordings. The mean difference between paired readings, expressed as a percentage of the average (SD) of each pair was 5·4 (4·7)%. Thus, the non-invasive measurement of linear cardiac output by Doppler ultrasound is similarly reproducible in vitro and in vivo and compares favourably with the measurement of volumetric cardiac output by thermodilution.

Non-invasive methods of measuring cardiac output using Doppler ultrasound have recently become available,[1 2] leading to the development of the concept of cardiac output as a distance.[3] Before measurement of linear cardiac output can be used with confidence, however, comparison with conventional volumetric cardiac output is needed. A newly introduced technique even if it is intrinsically highly reproducible may appear to perform badly if compared with a reference method that is unreliable.[4] We have described a method of assessing the accuracy and reproducibility of blood flow measurement by thermodilution using an artificial circulation in which absolute flow rate can be measured.[5] From the regression between the measurement of blood flow rate and its absolute value, the horizontal distance between the 95% confidence limits of a single prediction was calculated. This represented the range of flow rates that could give rise to an identical measurement; a change of flow rate has to exceed this figure to give rise to a change of measurement with 95% certainty. In this paper we describe how by incorporation of a pig aorta into the artificial circulation we were able to correlate absolute and Doppler ultrasound measurement of blood flow to give an assessment of the latter method's reproducibility and ability to detect a change of flow rate in terms directly comparable with thermodilution.

The reproducibility of linear cardiac output measurement made by Doppler ultrasound alone was also assessed from paired recordings in patients.

## Methods

### DOPPLER MEASUREMENT IN VITRO

An aorta was dissected from a large pig and after its side vessels had been tied off it was incorporated at point "C" into the artificial circulation previously described.[5] The aorta was allowed to assume its natural curvature while suspended in a dish of liquid paraffin. The ultrasound transducer was aligned tangentially to the arch and in line with the direction of midstream blood flow and recordings made at seven different pulsatile flow rates.

### DOPPLER MEASUREMENT IN VIVO

In 142 subjects aortic blood velocity was recorded over an average of 11·7 cardiac cycles using the Transcutaneous Aortic Velograph (TAV) Type

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Accepted for publication 17 September 1985

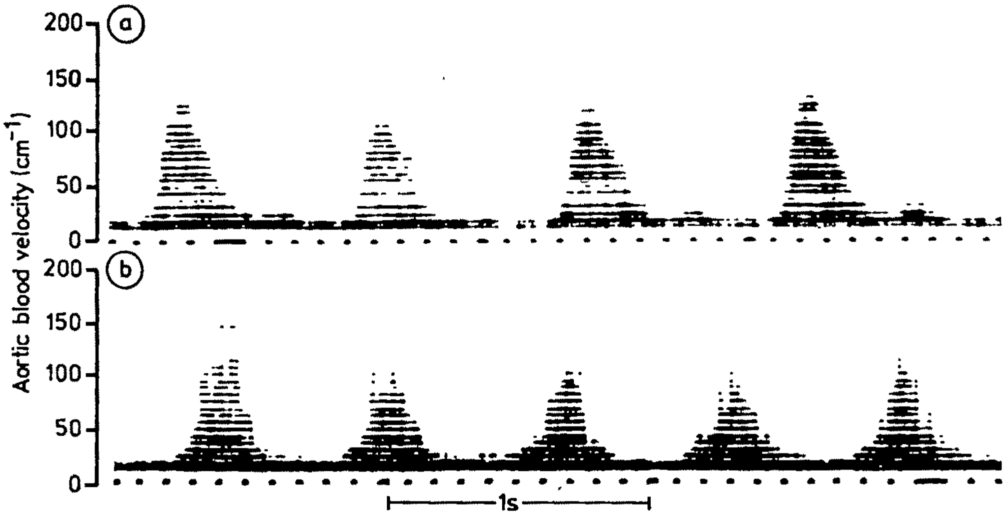

Fig. 1 *Doppler ultrasound recordings from a normal subject (a) and a pig aorta in an artificial circulation (b).*

1006 (Muirhead Medical Ltd) as described previously.[6] The recordings were made by one operator (F M McC) with the subject supine or in the left lateral position and they were then immediately repeated after removing and repositioning the transducer.

### INTERPRETATION OF DOPPLER RECORDINGS

Fig. 1 shows a typical in vivo trace (a) and (b) shows how similar it is to an in vitro trace. The velocity-time complexes are approximately triangular, and their outline represents the highest velocity recorded in the ultrasound path at any instant. The area within the velocity-time complex is recorded in cm as stroke distance, with the product of stroke distance and heart rate giving minute distance. For each in vivo recording peak aortic blood velocity and stroke and minute distances were averaged from 10–12 consecutive beats using our own curve-following programme with a Summagraphics Bitpad and Sirius microcomputer. The coefficient of variation of each of these measurements was also computed to show the extent of beat-to-beat variation. A mean of 17 consecutive pulses from each in vitro recording was digitised at each flow rate.

### REPRODUCIBILITY OF DIGITISING DOPPLER RECORDINGS

Sixty aortovelography recordings were digitised by the same person (MKD) on two occasions that were separated by an interval of several weeks and the results were compared. The electrocardiogram was not recorded and heart rate was estimated from the mean interval between the leading edges of consecutive velocity-time complexes. Another 50 aortovelography recordings were digitised twice by a second person (NEH).

### STATISTICAL METHODS

We used linear regression to relate actual blood flow and its measurement and to calculate the regression equation that was used to predict the measurement (± the standard error of prediction) that would be shown at a standard flow rate of 5 litres per minute.[7] The graphical results show the regression line together with the 95% confidence limits for a single prediction. The change of blood flow rate equivalent to the horizontal distance between the confidence limits was calculated and expressed as a percentage of 5 litres per minute.

The reproducibility of paired measurements was calculated as the difference between the greater and lesser measurements expressed as a percentage of the mean of the pair.

## Results

### COMPARISON OF IN VITRO DOPPLER AND FLOW RATE

Figure 2 shows the correlation between absolute flow rate and minute distance determined ultrasonically in a pig aorta included in the artificial circulation. The minute distance at each point on the regression line was derived from an average of 17 systolic velocity-time complexes and the standard

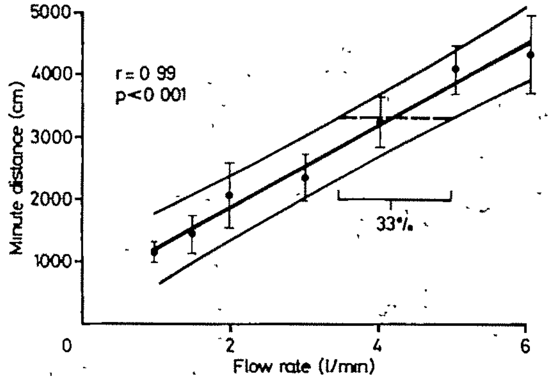

Fig. 2 *Regression line and 95% confidence limits of a single prediction for the measurement of minute distance against flow rate in a pig aorta in an artificial circulation. At each flow rate the mean (SE) of an average of 17·7 beats is indicated. Horizontal distance between confidence limits is expressed as a percentage of standard flow rate of 5 litres per minute.*

error of each mean is indicated; the mean pulse rate was 98 beats per minute. The correlation coefficient is 0·99 and the regression equation is $y = 572 + 2{\cdot}36\,x$. The standard error of the prediction at a flow rate of 5 litres per minute is 209 cm. This cannot be directly compared with flow rate but is 5·4% of the minute distance of 3850 cm predicted for a standard flow rate of 5 litres per minute. The 95% confidence limits at that flow rate are ±14%, and the horizontal distance between confidence limits expressed as a percentage of the standard flow rate is 33% of the standard flow rate or 1·65 litres per minute.

Table 1 *Mean beat-to-beat coefficient of variation and reproducibility (SD) of aortic blood velocity measurements in 142 paired recordings in vivo. The average number of complexes in each recording was 11·7 (2·1)*

| | *Coefficient of variation (%)* | *Reproducibility (%)* |
|---|---|---|
| Peak velocity | 4·2 (1·4) | 3·6 (2·8) |
| Heart rate | 5·7 (2·3) | 4·1 (3·7) |
| Stroke distance | 8·7 (2·5) | 5·2 (4·6) |
| Minute distance | 8·1 (2·8) | 5·4 (4·7) |

Table 2 *Mean reproducibility (SD) of digitising aortic blood velocity recordings on two occasions by two observers*

| | *Observer 1* | *Observer 2* |
|---|---|---|
| Peak velocity | 5·0 (7·1) | 4·6 (5·3) |
| Heart rate | 0·9 (0·7) | 0·9 (2·3) |
| Stroke distance | 5·5 (7·5) | 5·3 (4·8) |
| Minute distance | 5·7 (7·1) | 4·8 (4·5) |

### REPRODUCIBILITY OF IN VIVO DOPPLER MEASUREMENTS

Table 1 summarises the reproducibility of peak aortic blood velocity, heart rate, and stroke and minute distances in 142 paired measurements. The mean reproducibility of minute distance was 5·4%, but some of this variability arises from spontaneous fluctuation of cardiac output rather than its measurement. The mean reproducibility of heart rate (which is measured with an accuracy of >99%) was 4·1%, and the correlation between differences in minute distance and differences in heart rate had a coefficient of 0·4 ($p < 0{\cdot}001$); the proportion of variance in paired minute distance measurements that may be attributed to changes in heart rate is therefore at least 16%.

There is no consistent trend between the first and second measurements, except for peak aortic blood velocity which fell by <1% ($p < 0{\cdot}05$). Heart rate increased by <1 beat per minute ($p > 0{\cdot}05$). The mean beat-to-beat coefficient of variation is least for peak aortic blood velocity and greatest for stroke distance and is less than 10% in all cases.

### REPRODUCIBILITY OF DIGITISING DOPPLER RECORDINGS

Some of the differences between paired measurements could arise when the recordings are digitised and variability from this source is indicated in Table 2. Reproducibility is summarised for peak aortic blood velocity, heart rate, and stroke and minute distances for two observers who respectively digitised 50 and 60 recordings on two occasions. Reproducibility of heart rate measurements was < 1%, and that of the stroke and minute distances was about 5%.

## Discussion

### MEASUREMENT OF CARDIAC OUTPUT BY DOPPLER ULTRASOUND AND ECHOCARDIOGRAPHY

Several groups have shown that it is possible to measure left ventricular stroke volume, and hence cardiac output, non-invasively using the combination of Doppler ultrasound and echocardiography.[1 8-10] Stroke volume is calculated as the product of stroke distance and aortic cross sectional area. Stroke distance is not measured as such but can be calculated as the systolic-velocity integral at a point where the ultrasound beam is in line with the direction of flow. Ultrasound access from the suprasternal notch permits the measurement of stroke distance in the aortic root or in the aortic arch, which is the site we use, similar values being obtained at both sites.[11 12] The product of stroke distance and heart rate gives minute distance; stroke and minute distance are linear equivalents of stroke volume and cardiac output respectively.

There are three assumptions implicit in the method. Firstly, that stroke distance used in the calculation is representative of blood flow as a whole, as it would be only if the flow profile were flat. Since the flow profile in the aorta is skewed this assumption is only approximate. The second assumption is that total stroke volume passes the point at which stroke distance is measured. This too is not the case since a proportion of stroke volume enters the coronary circulation from the aortic root and a larger proportion is lost to the head and neck before velocity is measured in the aortic arch. The third assumption is also unwarranted; this is that the aortic cross section has a regular geometrical shape whose area can be readily calculated and that this remains constant throughout the cardiac cycle. Nevertheless, despite these three approximations it has been shown that there is close correspondence between stroke volumes determined in this way and by conventional invasive methods.

### MEASUREMENT OF CARDIAC OUTPUT BY DOPPLER ULTRASOUND ALONE

Thus, stroke volume approximates to the product of stroke distance and aortic cross sectional area or stroke distance approximates to stroke volume divided by aortic cross sectional area. Stroke distance is therefore related to stroke index; both are unidimensional, and both are corrected for variation in body size; the former in effect by division of stroke volume by aortic cross sectional area, the latter by division by body surface area. Stroke distance would therefore be expected to be proportional to stroke volume within subjects,[13-16] to be independent of body size,[2] and its product with heart rate (that is minute distance) should provide an absolute measure of cardiac output.[6] All three expectations of the measurement have been fulfilled. Use of this linear measure to assess cardiac output obviates the need to measure aortic cross sectional area which is technically the most demanding part of the procedure and the part which is associated with the greatest error.[12] When linear cardiac output alone is calculated and compared with a normal range of values none of the three assumptions involved in conversion of velocity measurements to volume is made.[3]

Whereas the weakness of thermodilution is its performance during pulsatile flow,[5] the strength of the Doppler ultrasound method of measuring cardiac output that we describe is its ability to measure beat-to-beat changes of velocity. The beat-to-beat coefficient of variation ranges from 4·2% for peak aortic blood velocity to 8·7% for stroke distance. Thus for a recording of 10 beats the standard error of the mean for stroke distance is 2·8% falling to 1·9% for a recording of 20 beats. For most purposes a 10 beat recording provides a sufficiently accurate estimate of minute distance. Distante *et al* using aortovelography found a beat-to-beat coefficient of variation for time averaged velocity (corresponding to minute distance/60) of 10%.[16]

### REPRODUCIBILITY OF DOPPLER ULTRASOUND MEASUREMENTS

The main sources of imprecision in the measurement of linear cardiac output are alignment of the ultrasound beam and the signal to noise ratio. The measured velocity of blood flow is proportional to the cosine of the angle between the direction of the ultrasound beam and the direction of blood flow. Since the cosine of an angle $<18°$ is $>0·95$ there is an angular latitude of 36° for $<5\%$ underestimation of velocity. The transcutaneous aortovelograph used by us generates a broad beam of continuous ultrasound which detects movement at any distance from the transducer, subject only to the attenuation of ultrasound by transmission through tissue. By recording velocities in the aortic arch correct positioning of the transducer is assured since axial flow is almost certain to be aligned with the ultrasound beam at some point around the arch. Correct alignment is aided by selecting the position which gives the highest pitch of audible Doppler shift frequencies and the greatest velocity on the on-line paper record.

Recognition of the maximum velocity of movement within the ultrasound beam may be achieved by electronic signal processing that provides an analogue signal proportional to the greatest frequency shift detected at any moment.[17] This method, however, does not differentiate between forward or reverse flow and is prone to artefactual error. Spectral analysis of the signal is more satisfactory since this gives the velocity spectrum and allows recognition of turbulence and separation of forward and reverse flow. Our equipment uses spectral analysis, the amplitude of each frequency band (and hence velocity) being recorded on a grey scale by a separate pen. Reproducible recognition and integration of maximal velocity requires accurate edge detection of the velocity-time complex which depends on a satisfactory signal to noise ratio.

The leading edges of the velocity-time complexes recorded by aortovelography are easily recognised and the distance from one leading edge to the next is used to calculate mean heart rate. Reproducibility of mean heart rate in paired digitised measurements of the same records was <1%. Peak aortic blood velocity, marked by the apex of the triangular shaped velocity-time complex, had a digitising reproducibility of about 5%, and that of stroke distance, measured as the area of the triangle, was <6%. In paired recordings the worst reproducibility of any measurement was 5·4% for minute distance in which imprecision in the measurements of flow time, peak aortic blood velocity, heart rate, and the process of digitising are all compounded. Peak aortic blood velocity was the most reproducible measurement, with an average difference of 4% between paired readings (Table 2).

This degree of reproducibility of aortovelography in vivo is consistent with that found by us in vitro. The 95% confidence limits for minute distance at a flow rate of 5 litres per minute in vitro were ±14%. The 95% confidence limits for reproducibility in vivo are about 15%, there being little difference between the two figures despite short term changes in flow rate and repositioning the transducer between measurements in vivo. Fraser *et al* measured mean blood velocity in adults by aortovelography with reproducibility of 6·4% with the same observer and 7·4% with different observers.[18] Using a pulsed Doppler system Gisvold and Brubakk obtained a coefficient of variation within subjects of 6–11% for all velocity measurements in the aortic arch.[11]

Gardin *et al* used a range gated Doppler ultrasound technique to measure blood flow in the ascending aorta.[19] Reproducibility of measurement of the Doppler records was 2·5% for peak aortic blood velocity, 1·9% for ejection time, and 3·2% for the flow velocity integral or stroke distance, the latter being calculated from electronic measurement of the former without planimetry. Day to day reproducibility was 3·8 (3·1)% for stroke distance. Hatle and Angelsen reported that the reproducibility of the integral under the maximal velocity curve was 9·1% in paired measurements separated by days or months.[20]

### MEASUREMENT OF A CHANGE OF CARDIAC OUTPUT

The most important clinical application of cardiac output measurement is the recognition of a change, particularly a fall, of cardiac output. A change of cardiac output may be measured under three circumstances. Firstly, when any number of measurements may be made before and after an intervention. The ability to detect a change is then only limited by the number of measurements made before and after its occurrence. Secondly, a sufficient number of measurements may have been made before the change to establish a mean cardiac output and its standard deviation. A single measurement taken after an intervention that is more than two standard deviations from the previously established mean may be taken to have resulted from a true haemodynamic change. The third situation is when the standard deviation of the current series of measurements is not known and has to be assumed to be similar to previous experience. Two single measurements can only be assumed to have resulted from a changed cardiac output if they differ by more than four standard deviations. This is the situation described in this and the preceding paper.[5]

In comparing the performance of different methods of measuring cardiac output the standard deviation of the measurement is inadequate by itself—what is important is the variation of flow rate which gives rise to a change of measurement. This is why we have suggested the horizontal distance between confidence limits since this combines a measure of variability of the measurement, that is the confidence limits of a single prediction, with the slope of the regression line which relates flow rate and its measurement. From a reproducibility study alone the extent of the haemodynamic change that has given rise to a change in measurement of flow rate cannot be known without an independent measure of blood flow.

In vitro the range of blood flow rate that could give rise to an identical measurement by Doppler ultrasound was 1·65 litres per minute, that is 33% of the standard flow rate. A greater change of flow rate than this would be necessary for 95% certainty of a difference between two single measurements. This compares with 21–33% for three different makes of thermodilution cardiac output computer under optimal conditions in vitro, and 30–62% overall. The percentage vertical spread of the confidence limits for aortovelography is similar to that of the cardiac output computer with the least variability but the horizontal distance between confidence limits depends also on the slope of the regression line. All of the regression lines for cardiac output computers had slopes >1 and passed below the origin whereas for aortovelography the slope is <1 and passes above the origin. This has the effect of reducing the sensitivity of aortovelography to measure a change of flow rate compared with thermodilution where overestimation of absolute flow rate increases the ability to detect change.

### EFFECT OF BLOOD PRESSURE ON AORTIC BLOOD VELOCITY

In our circulation model blood pressure was not controlled, so that as flow rate was reduced blood pressure fell resulting in reduction of the cross sectional area of the pig aorta and a less than proportionate fall of velocity and the velocity-integral. Thus, when a flow rate of 5 litres per minute was halved, minute distance was reduced to 57% of the initial value; the predicted value of minute distance for zero flow was 572 cm. Light has calculated that if in man the same reduction of cardiac output from 5 to 2·5 litres per minute is accompanied by a fall of systolic blood pressure of 45 mm Hg, aortic blood velocity would fall to 58% of its previous value.[21] This suggests that the compliance of the pig aorta used in vitro is similar to that of the aorta in intact man.

The extent of the influence of blood pressure on aortic blood velocity needs clarification. In hypertensive patients aortic blood velocity is reduced compared with normal controls,[6] but this could be due either to an increased aortic arch diameter[22] or to reduced cardiac output,[23] both of which have been demonstrated in hypertension. In non-hypertensive normal subjects aortic blood velocity was independent of blood pressure.[2] In dogs aortic diameter correlated with cardiac output, but the graph relating cardiac output (measured as the product of aortic cross sectional area and systolic velocity integral) and absolute flow rate went virtually through the origin.[12] It seems likely then that fluctuation of blood pressure within the normal range has little effect on aortic blood velocity, but the ability of aortovelography to detect a fall of cardiac output is slightly reduced by any large accompanying fall of blood pressure.

## CONCLUSIONS

Cardiac output is the ultimate expression of cardiovascular function and there are many clinical circumstances where its measurement is desirable. The standard technique for measuring cardiac output is thermodilution which is technically difficult, costs about £100 per patient in disposable items,[24] and carries a risk of serious complications.[25] Our experiments have shown that under optimum conditions of pulsatile flow in vitro thermodilution provides an unreliable estimate of absolute flow rate and detects 21–33% changes of flow rate with 95% certainty and with a reproducibility that is seldom better than 10%. The method is unlikely to perform as well as this under clinical conditions.

The non-invasive measurement of linear cardiac output by Doppler ultrasound is simple, without risk or discomfort, and has negligible running costs. In vitro the method detects a 33% change of flow rate with 95% certainty. In the absence of aortic disease the absolute value of linear cardiac output is meaningful,[6] and under clinical conditions its measurement has a reproducibility of about 5%.

F M McL is research fellow of the Association of Anaesthetists of Great Britain and Ireland. M K D was supported by the Scottish Home and Health Department with a Medical Student Vacation Research Grant. We are also grateful to Grampian Health Board for a research grant.

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# Measurement of aortic regurgitation by Doppler echocardiography

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SUMMARY In an attempt to develop a new approach to the non-invasive measurement of aortic regurgitation, transmitral volumetric flow (MF) and left ventricular total stroke volume (SV) were measured by Doppler and cross sectional echocardiography in 23 patients without aortic valve disease (group A) and in 26 patients with aortic regurgitation (group B). The transmitral volumetric flow was obtained by multiplying the corrected mitral orifice area by the diastolic velocity integral, and the left ventricular total stroke volume was derived by subtracting the left ventricular end systolic volume from the end diastolic volume. The aortic regurgitant fraction (RF) was calculated as: $RF = 1 - MF/SV$. In group A there was a close agreement between the transmitral volumetric flow and the left ventricular total stroke volume, and the difference between the two measurements did not differ significantly from zero. In group B the left ventricular total stroke volume was significantly larger than the transmitral volumetric flow, and there was good agreement between the regurgitant fractions determined by Doppler echocardiography and radionuclide ventriculography. Discrepancies between the two techniques were found in patients with combined aortic and mitral regurgitation or a low angiographic left ventricular ejection fraction ($<35\%$). The effective cardiac output measured by Doppler echocardiography accorded well with that measured by the Fick method.

Doppler echocardiography provides a new and promising approach to the non-invasive measurement of aortic regurgitation.

The importance of measuring aortic regurgitation has been recognised for more than 150 years,[1] but a suitable technique is still lacking. Invasive techniques have limitations which preclude their use in serial evaluation.[2 3] Among the non-invasive techniques, radionuclide ventriculography has proved to be an accurate method for measuring aortic regurgitation but has the disadvantages of high cost and of requiring exposure to radiation.[4 5] Recently, Doppler echocardiography has been used to assess aortic regurgitation, but the proposed approaches are still semiquantitative.[6-8]

The regurgitant volume must be known before aortic regurgitation can be assessed.[9] It is now possible to measure the transmitral volumetric flow by Doppler echocardiography[10-12] and the left ventricular total stroke volume by cross sectional echocardiography.[13-15] Theoretically, the two volume measurements should be equal when the left ventricular diastolic inflow comes solely through the mitral orifice. If, however, the left ventricular diastolic inflow comes through both the aortic and mitral valves, as in aortic regurgitation, the two measurements will differ with the difference being equal to the aortic regurgitant volume. The present study was undertaken to test this assumption in patients with a normal aortic valve and in those with aortic regurgitation. We compared results obtained by Doppler echocardiography with those obtained by radionuclide ventriculography and cardiac catheterisation.

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Accepted for publication 10 September 1985

Table 1 *Results of Doppler echocardiography in group A*

| *Case* | *Diagnosis* | *CMA (cm²)* | *DVI (cm)* | *MF (cm³)* | *EDV (cm³)* | *ESV (cm³)* | *SV (cm³)* | *RF (%)* |
|---|---|---|---|---|---|---|---|---|
| 1 | CCM + MR | 2·99 | 15·7 | 47 | 261 | 218 | 43 | −9·3 |
| 2 | CAD | 3·67 | 18·5 | 68 | 339 | 267 | 72 | 5·6 |
| 3 | PE | 4·18 | 17·4 | 73 | 177 | 105 | 72 | −1·4 |
| 4 | CAD | 5·13 | 16·9 | 87 | 224 | 128 | 96 | 9·4 |
| 5 | CAD | 3·96 | 18·9 | 75 | 130 | 58 | 72 | −4·2 |
| 6 | N | 3·69 | 18·8 | 69 | 221 | 140 | 81 | 14·8 |
| 7 | CAD | 4·86 | 14·4 | 70 | 129 | 69 | 60 | −16·7 |
| 8 | N | 5·62 | 11·8 | 66 | 123 | 53 | 70 | 5·7 |
| 9 | CAD | 5·27 | 17·1 | 90 | 209 | 127 | 82 | −9·8 |
| 10 | N | 4·26 | 24·7 | 105 | 204 | 106 | 98 | −7·1 |
| 11 | CAD | 3·35 | 20·8 | 70 | 334 | 267 | 67 | −4·5 |
| 12 | PS | 4·78 | 23·5 | 112 | 194 | 86 | 108 | −3·7 |
| 13 | HCM | 5·20 | 16·4 | 85 | 179 | 94 | 85 | 0 |
| 14 | CAD | 4·76 | 18·2 | 87 | 410 | 320 | 90 | 3·3 |
| 15 | N | 4·60 | 17·6 | 81 | 109 | 33 | 76 | −6·6 |
| 16 | MR | 6·12 | 19·6 | 120 | 235 | 104 | 131 | 8·4 |
| 17 | AVR | 4·05 | 19·4 | 79 | 216 | 124 | 92 | 14·1 |
| 18 | N | 4·37 | 23·0 | 100 | 170 | 70 | 100 | 0 |
| 19 | PE | 6·89 | 15·1 | 104 | 159 | 65 | 94 | −10·6 |
| 20 | N | 5·48 | 24·0 | 132 | 222 | 91 | 131 | −1·0 |
| 21 | PS | 4·66 | 18·7 | 87 | 144 | 62 | 82 | −6·1 |
| Mean (SD) | | 4·66<br>(0·93) | 18·6<br>(3·3) | 86<br>(20) | 209<br>(77) | 123<br>(79) | 86<br>(21) | −0·92<br>(8·3) |

CMA, corrected mitral orifice area, DVI, diastolic velocity integral, MF, transmitral volumetric flow; EDV, left ventricular end diastolic volume; ESV, left ventricular end systolic volume; SV, left ventricular total stroke volume; RF, aortic regurgitant fraction; CCM, congestive cardiomyopathy; MR, mitral regurgitation; CAD, coronary artery disease; N, normal, PE, pericardial effusion; PS, pulmonary stenosis, HCM, hypertrophic cardiomyopathy; AVR, prosthetic aortic valve replacement.

## Patients and methods

### PATIENTS

Forty nine patients who underwent diagnostic cardiac catheterisation gave their informed consent to the study. They were divided into two groups according to clinical and angiographic findings. Group A consisted of 23 patients (17 men and six women, ranging in age from 17 to 65 years, mean 57) without evidence of aortic valve disease. Group B consisted of 26 patients (18 men and eight women, ranging in age from 17 to 76 years, mean 52) with aortic regurgitation. Tables 1 and 2 give the clinical diagnoses in both groups. None of these patients had mitral stenosis and all had a normal left ventricular wall motion except for a few cases with a generalised left ventricular hypokinesia. In group B, 14 patients had pure aortic regurgitation and 12 had concomitant valve lesions. The angiographic left ventricular ejection fraction was normal ($\geqslant 50\%$) in 22 patients and significantly reduced ($\leqslant 35\%$) in four. All patients were in sinus rhythm. Doppler echocardiography, radionuclide ventriculography, and cardiac catheterisation were performed independently by different investigators and the results were not compared until after the study was completed.

### DOPPLER ECHOCARDIOGRAPHY

Transmitral volumetric flow and left ventricular total stroke volume were measured independently by two different investigators. A phased array sector scanner (IREX III) with a wide scanning angle of 80° and a 2·5 MHz transducer was used for echocardiographic recordings. A multifrequency (1–10 MHz) Doppler instrument (ALFRED, Vingmed) with both continuous and pulsed modes and a 2 MHz transducer were used for velocity measurement. In the pulsed mode the sample volume is about 8 mm in diameter and 5 mm in length. The received signals were processed by two frequency estimators and converted into analogue voltage in proportion to the mean and maximum Doppler frequency shifts. A direct audio output aided the identification of the best transducer position. Calculations were performed by means of a graph pen microcomputer system (CARDIO 80, Kontron).

### MEASUREMENT OF THE TRANSMITRAL VOLUMETRIC FLOW

Transmitral volumetric flow was measured by our previously described technique.[11] The maximal mitral orifice area in early diastole was measured by cross sectional echocardiography from the left parasternal short axis view. A derived M mode echocardiogram of the mitral valve was digitised to obtain the mitral orifice opening ratio.[11] The corrected mitral orifice area (CMA) was calculated by multiplying the maximum mitral orifice area by the opening ratio. The Doppler transducer was placed at the apex and the fastest velocities of the transmitral flow were recorded with the pulsed mode at a position where the mitral valve opening was clearly

Table 2 *Results of Doppler echocardiography in group B*

| *Case* | *Diagnosis* | *CMA ($cm^2$)* | *DVI (cm)* | *MF ($cm^3$)* | *EDV ($cm^3$)* | *ESV ($cm^3$)* | *SV ($cm^3$)* | *RF (%)* |
|---|---|---|---|---|---|---|---|---|
| 1 | AR + AS | 3·62 | 21·6 | 78 | 241 | 72 | 169 | 54 |
| 2 | AR | 3·26 | 22·7 | 74 | 377 | 169 | 208 | 64 |
| 3 | AR | 5·46 | 21·6 | 118 | 483 | 188 | 295 | 60 |
| 4 | AR + MR | 3·67 | 35·6 | 131 | 408 | 143 | 265 | 51 |
| 5 | AR | 1·75 | 43·7 | 76 | 371 | 176 | 195 | 61 |
| 6 | AR | 4·84 | 18·8 | 91 | 412 | 182 | 230 | 60 |
| 7 | AR | 2·89 | 21·6 | 62 | 168 | 86 | 82 | 24 |
| 8 | AR | 6·28 | 14·9 | 94 | 342 | 193 | 149 | 37 |
| 9 | AR | 3·81 | 22·5 | 86 | 264 | 114 | 150 | 43 |
| 10 | AR | 2·41 | 22·4 | 54 | 246 | 127 | 119 | 55 |
| 11 | AR + AS + MR | 5·23 | 21·2 | 111 | 276 | 97 | 179 | 38 |
| 12 | AR + AS | 4·44 | 19·6 | 87 | 272 | 127 | 145 | 40 |
| 13 | AR + AS + MR + TR | 2·25 | 33·8 | 76 | 360 | 253 | 107 | 29 |
| 14 | AR + MR | 3·38 | 14·2 | 48 | 274 | 189 | 85 | 44 |
| 15 | AR | 4·24 | 22·0 | 93 | 423 | 203 | 220 | 58 |
| 16 | AR | 3·44 | 19·9 | 68 | 296 | 130 | 166 | 59 |
| 17 | AR + AS | 3·27 | 20·4 | 67 | 215 | 140 | 75 | 11 |
| 18 | AR | 3·33 | 27·4 | 91 | 294 | 123 | 171 | 47 |
| 19 | AR + MR | 4·05 | 25·5 | 103 | 334 | 160 | 174 | 41 |
| 20 | AR + AS | 4·02 | 25·7 | 103 | 344 | 137 | 207 | 50 |
| 21 | AR | 3·26 | 27·8 | 90 | 486 | 200 | 286 | 68 |
| 22 | AR + AS | 3·57 | 21·2 | 76 | 149 | 46 | 103 | 26 |
| 23 | AR + AS | 3·44 | 23·9 | 82 | 211 | 88 | 123 | 33 |
| 24 | AR | 5·23 | 17·6 | 92 | 199 | 83 | 116 | 21 |
| 25 | AR | 3·32 | 15·9 | 53 | 279 | 219 | 60 | 12 |
| Mean (SD) | | 3·78<br>(1·04) | 23·3<br>(6·6) | 84<br>(20) | 309<br>(91) | 145<br>(51) | 163<br>(65) | 43<br>(16) |

AR, aortic regurgitation; AS, aortic stenosis, TR, tricuspid regurgitation. See Table 1 for other abbreviations.

heard. In cases with severe aortic regurgitation and mitral valve fluttering the velocities were measured 1 cm above the level of the mitral valve opening. Care was taken to avoid the regurgitant jet and to reduce the effect of the mitral valve fluttering while still measuring the fastest transmitral flow. The maximal velocity curves of the mitral flow were integrated to obtain the diastolic velocity integral (DVI). Assuming that the angle between the Doppler beam and the mitral flow is zero, the transmitral volumetric flow (MF) was calculated as: $MF = CMA \times DVI$. The effective cardiac output (CO) in the presence of aortic regurgitation in group B was calculated as: $CO = MF \times HR$, where HR is the heart rate during Doppler study. At least six beats were averaged to obtain all the variables.

### MEASUREMENT OF LEFT VENTRICULAR TOTAL STROKE VOLUME

With the transducer at the apex the apical four chamber view was recorded by cross sectional echocardiography focusing on the left ventricle. To avoid foreshortening of the left ventricle the transducer was moved along in three spatial directions—that is caudally and cranially to reach the most apical position, dorsally and ventrally to image the maximum left ventricular long axis, and medially and laterally to obtain the maximum short axis. All images were recorded on video tapes. The frames with the largest and smallest left ventricular cavity size within one cardiac cycle were selected to calculate the end diastolic and end systolic volume respectively. The inner edges of the endocardial echoes were traced and if there was echo dropout a straight line was drawn between the two adjacent echoes. The programme used for volume (V) computation is based on the area-length method[16] as: $V = 8A^2/3\pi L$, where A is the area of the left ventricular cavity and L is the left ventricular long axis which was taken as running from the junction of the septum and the mitral valve to the apex. The left ventricular total stroke volume (SV) was then calculated as: $SV = EDV - ESV$, where EDV is the left ventricular end diastolic volume and ESV is the end systolic volume. Five to seven beats were digitised and the values were averaged.

Theoretically, in patients without aortic regurgitation the transmitral volumetric flow (MF) should equal left ventricular total stroke volume (SV). In patients with aortic regurgitation the difference between the two measurements should equal the aortic regurgitant volume. The aortic regurgitant fraction (RF) was thus calculated in both groups as: $RF = 1 - MF/SV$.

### RADIONUCLIDE VENTRICULOGRAPHY

Gated blood pool imaging was performed within 24 hours of Doppler echocardiography in group B by means of a GE scintillation camera (400 T AZS) interfaced to a GE STAR computer system. Erythrocytes were labelled by a combined in vivo and in vitro method. With the patient in a supine position the detector was located in the 40° left anterior projection with 15° caudal tilt to optimise a four chamber view. Under the STAR computer's PAGE multigated cardiac protocol 300 heart beats were stored in frame mode. Both left and right ventricular activity curves were analysed by an identical automatic technique including phase analysis for variable regions of interest and background area selection. In some cases operator intervention was necessary to achieve separation of the images of the right ventricle and right atrium. Separate regions of interest for end diastole and end systole were used to calculate ventricular stroke counts. The aortic regurgitant fraction (RF) was calculated as: $RF = 1 - RVSC/LVSC$, where RVSC is the right ventricular stroke count and LVSC the left ventricular stroke count. Because the mean left to right ventricular stroke count ratio in patients without valvar heart disease is 1·12 in this laboratory, the regurgitant fraction was corrected by multiplying the right ventricular stroke count by 1·12.

### CARDIAC CATHETERISATION

All patients underwent left heart catheterisation. In addition, right heart catheterisation was performed 24 hours before or 24 hours after Doppler echocardiography in 23 patients in group B. Cardiac output was measured according to the Fick method.

### STATISTICAL ANALYSIS

Methods were compared by the statistical method of Altman and Bland[17] and by paired and unpaired $t$ tests. Data were expressed as mean (1 SD).

## Results

### DOPPLER ECHOCARDIOGRAPHY

Technically adequate Doppler echocardiographic recordings were obtained in 21 (91%) patients in group A and in 25 (96%) patients in group B. Two patients in group A were excluded because of suboptimal echocardiographic images and one patient in group B was excluded due to unsatisfactory Doppler velocity recordings. Tables 1 and 2 list the individual results in the remaining 21 patients in group A and 25 patients in group B. In group A the transmitral volumetric flow ranged from 47 to 132 cm$^3$ (86 (20) cm$^3$) and the left ventricular total stroke volume from 43 to 131 cm$^3$ (86 (21) cm$^3$). In group B the transmitral volumetric flow ranged from 48 to 131 cm$^3$ (84 (20) cm$^3$) and the left ventricular total stroke volume from 60 to 295 cm$^3$ (163 (65) cm$^3$).

### RADIONUCLIDE VENTRICULOGRAPHY

Technically adequate radionuclide images were obtained in 25 (96%) patients in group B while one patient was excluded because of unsatisfactory separation of the right ventricle from the right atrium. In the 25 patients the left ventricular ejection fraction ranged from 26% to 74% (57 (15)%) and the right ventricular ejection fraction from 23% to 62% (46 (11)%). Mean aortic regurgitant fraction was 44% (19) (range 0%–67%). In two cases (17 and 25) in group B regurgitant fraction was zero and the angiographic left ventricular ejection fraction was low (<35%).

### COMPARISON BETWEEN TRANSMITRAL VOLUMETRIC FLOW AND LEFT VENTRICULAR TOTAL STROKE VOLUME

In group A there was a close agreement between the two measurements. The difference between the two measurements did not correlate with the mean of the two measurements and did not differ significantly from zero (Fig. 1). The relative bias calculated from the mean difference between the two measurements was 0·24 cm$^3$ and the estimate of error calculated from the standard deviation of these differences was 6·96 cm$^3$. The agreement between the two measurements was not affected by mitral regurgitation

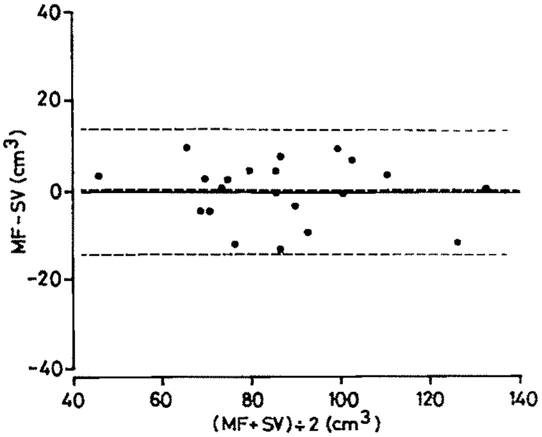

Fig 1 *Difference between the transmitral volumetric flow and the left ventricular total stroke volume (MF − SV) is plotted against the mean of the two measurements (MF + SV) − 2) in group A. Broken lines indicate the mean and the 95% range of the differences between the two measurements. This type of plot allows an easier and better assessment of the difference between two methods than conventional correlation and regression analysis.*[17] *The difference between methods (MF − SV) is independent of the size of measurement (MF + SV) − 2) and does not differ significantly from zero. The relative bias and the estimate of error are 0·24 cm$^3$ and 6 96 cm$^3$ respectively.*

present in two cases (1 and 16) in group A. The aortic regurgitant fraction was −0·92% (8·3)% (range −16·7%–14·1%). In group B the left ventricular total stroke volume was larger than the transmitral volumetric flow in all cases and there was a significant difference between the two measurements (163 (65) cm$^3$ *vs* 84 (20) cm$^3$, $p<0{\cdot}001$). The aortic regurgitant fraction was 43 (16)% (range 11%–68%).

### COMPARISON BETWEEN DOPPLER ECHOCARDIOGRAPHY AND RADIONUCLIDE VENTRICULOGRAPHY

The results of Doppler echocardiography were compared with those of radionuclide ventriculography in 24 patients in group B in whom both recordings were adequate. The difference between the regurgitant fractions determined by Doppler and radionuclide techniques did not correlate with the mean of the two measurements and did not differ significantly from zero (Fig. 2). The relative bias was 0·21% and the estimate of error was 10·5%. In five patients with combined aortic and mitral regurgitation (two of whom also had an angiographic left ventricular ejection fraction <35%) the regurgitant fractions by radionuclide technique were considerably higher than those derived from Doppler echocardiography. When these five patients were excluded, there was a good agreement between the two measurements, with the relative bias and the estimate of error being 3·5% and 6·4% respectively. The results obtained by the two techniques differed in the two patients with a low angiographic left ventricular ejection fraction (<35%) in whom the regurgitant fraction by radionuclide ventriculography was zero, but concomitant aortic stenosis did not adversely affect the agreement between results obtained by the two techniques.

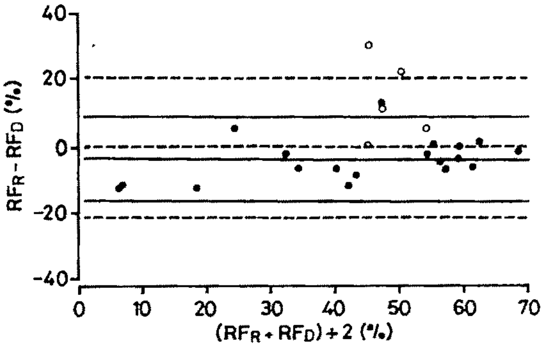

Fig. 2 *Difference between the regurgitant fractions determined by radionuclide and Doppler techniques ($RF_R - RF_D$) vs the mean of the two measurements (($RF_R + RF_D$) ÷ 2) in group B. The broken lines show the mean and the 95% range of the differences between the two measurements in the whole group. The solid lines show the mean and the 95% range of the differences between the two measurements in patients without mitral regurgitation. The difference between methods ($RF_R - RF_D$) is independent of the size of measurement (($RF_R + RF_D$) − 2) and does not differ significantly from zero. The relative bias and the estimate of error are 0·21% and 10·5% in the whole group and 3·5% and 6·4% in patients without mitral regurgitation respectively. Closed circles, aortic regurgitation; open circles, aortic and mitral regurgitation.*

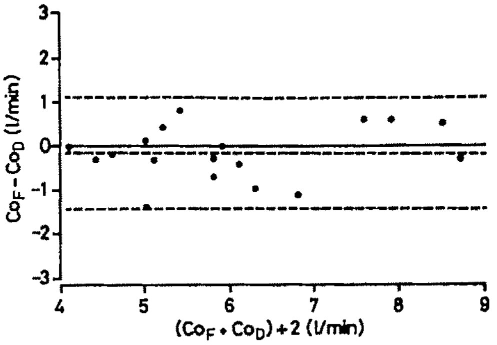

Fig. 3 *Difference between the effective cardiac output measured by Doppler echocardiography and Fick method ($Co_F - Co_D$) vs the mean of the two measurements (($Co_F + Co_D$) ÷ 2 in group B. Broken lines indicate the mean and the 95% range of the differences between the two measurements. The difference between methods ($Co_F - Co_D$) is independent of the size of measurement (($Co_F + Co_D$) ÷ 2) and does not differ significantly from zero. The relative bias and the estimate of error are 0·16 l/min and 0·62 l/min respectively.*

### COMPARISON BETWEEN DOPPLER ECHOCARDIOGRAPHY AND CARDIAC CATHETERISATION

The effective cardiac output determined by Doppler echocardiography was compared with that obtained by the Fick method in 18 patients in group B without mitral regurgitation who underwent right heart catheterisation. There was a good agreement between the two techniques. The difference between the two measurements did not correlate with the mean of the two measurements and did not differ significantly from zero (Fig. 3). The relative bias and the estimate of error were 0·16 l/min and 0·62 l/min respectively.

## Discussion

The size of the aortic regurgitant volume depends on the cross sectional area of the valve defect, the diastolic pressure gradient across the aortic valve, and the duration of diastole.[9] Although Doppler echocardiography has been used to estimate these determinants, direct measurement of the regurgitant volume has proved difficult.[6-8] In the present study the aortic regurgitant volume was calculated as the difference between the left ventricular total stroke volume as measured by cross sectional echocardiography and the transmitral volumetric flow measured by Doppler technique. The accuracy of this method is dependent upon that of the two combined measurements. The transmitral volumetric flow measurement by Doppler echocardiography has been validated by us and other workers against established invasive techniques.[10-12] As a result of aortic regurgitation the mitral orifice area in group B tended to be smaller than that in group A, resulting in an increased diastolic velocity integral. All of our patients, however, had a maximal mitral orifice area larger than that in mitral stenosis ($<2{\cdot}5\ cm^2$).[18] Although both the regurgitant jet and the transmitral flow come towards the transducer during diastole, differences in the quality of audio signals, the timing of flow velocities, and the position of sample volumes make the distinction between the two flows relatively easy. The effect of mitral valve fluttering can be minimised by adjusting the position of the sample volume in the mitral flow canal, since small changes in sample volume position do not significantly affect the transmitral volumetric flow measurement.[11] The good agreement between the effective cardiac output determined by Doppler echocardiography and the Fick method demonstrates that the transmitral volumetric measurement is still valid even in the presence of aortic regurgitation.

Measurement of the left ventricular volume by cross sectional echocardiography has proved reasonably accurate in the absence of regional left ventricular wall dyskinesia.[13-15] Because the four chamber view can be easily obtained in most adult patients, we used this view and the area-length formula to calculate the left ventricular volume. The fact that a known left ventricular volume is consistently overestimated by the area-length formula in angiography,[19 20] while it is often underestimated by the same formula in echocardiography,[21] indicates that the most important pitfall in volume measurement by cross sectional echocardiography is the foreshortening of the left ventricle rather than the geometric assumption.[22] Therefore, we made great efforts to avoid foreshortening of the left ventricle in this study. The good results obtained in the study indicate that left ventricular total stroke volume can be reliably estimated by cross sectional echocardiography.

Combining the transmitral volumetric flow and the left ventricular total stroke volume measurements offers several advantages for determining the regurgitant volume. Firstly, use of cross sectional echocardiography to measure the left ventricular total stroke volume avoids the difficulties in determining the aortic volumetric flow by Doppler technique in patients with a dilatated ascending aorta.[23] Secondly, the volume measurement by cross sectional echocardiography is not affected by the concomitant aortic stenosis, where the aortic volumetric flow measurement becomes invalid.[23] Thirdly, in patients with combined aortic and mitral regurgitation, the volume measurement by cross sectional echocardiography still gives the total stroke volume, whereas the aortic volumetric flow measurement by Doppler technique gives only a part of it. Finally, the difference between the left ventricular total stroke volume and the transmitral volumetric flow equals the aortic regurgitant volume, whether aortic regurgitation is isolated or associated with other valvar regurgitation. If the left ventricular total stroke volume is related to the transpulmonary[24] or transtricuspid[25] volumetric flow, the aortic regurgitant volume can be calculated only in isolated aortic regurgitation.

Radionuclide ventriculography has been accepted as a reliable technique for measuring aortic regurgitation.[26-28] The good agreement between regurgitant fractions determined by Doppler and radionuclide techniques in patients with isolated aortic regurgitation indicates that our Doppler echocardiographic method is as reliable as radionuclide ventriculography in the non-invasive measurement of aortic regurgitation. The major discrepancies between the two techniques were found in patients with combined aortic and mitral regurgitation or a low left ventricular ejection fraction ($<35\%$). This is due to the fact that the radionuclide technique calculates the regurgitant volume as the difference between the left and right ventricular stroke volume, while our Doppler method calculates it as the difference between the left ventricular total stroke volume and the transmitral volumetric flow. Thus in patients with combined aortic and mitral regurgitation, the regurgitant fraction by the radionuclide technique is the sum of both aortic and mitral regurgitant fractions,[26] while our method still gives the real aortic regurgitant fraction. In one of these cases, however, a small concomitant degree of tricuspid regurgitation may have been a potential source of error in determination of the regurgitant fraction by the radionuclide technique.[26] Another major limitation of the radionuclide technique is the inaccuracy in determining the regurgitant fraction in patients with a low left ventricular ejection fraction.[29] Doppler echocardiography is probably more accurate than radionuclide techniques for measuring aortic regurgitation in patients with concomitant mitral regurgitation or impaired left ventricular function.

There are two major limitations to our method. It is difficult to measure transmitral volumetric flow when a mitral flow is disturbed, as in mitral stenosis or pronounced mitral valve fluttering. Similarly, measurement of left ventricular total stroke volume measurement is subject to errors in cases with concomitant left ventricular regional wall dyskinesia. Despite these limitations our Doppler echocardiographic method offers a new and promising approach to the non-invasive measurement of aortic regurgitation.

Y Z is a research fellow from the Cardiovascular Institute, Shandong Medical College, Jinan, People's Republic of China.

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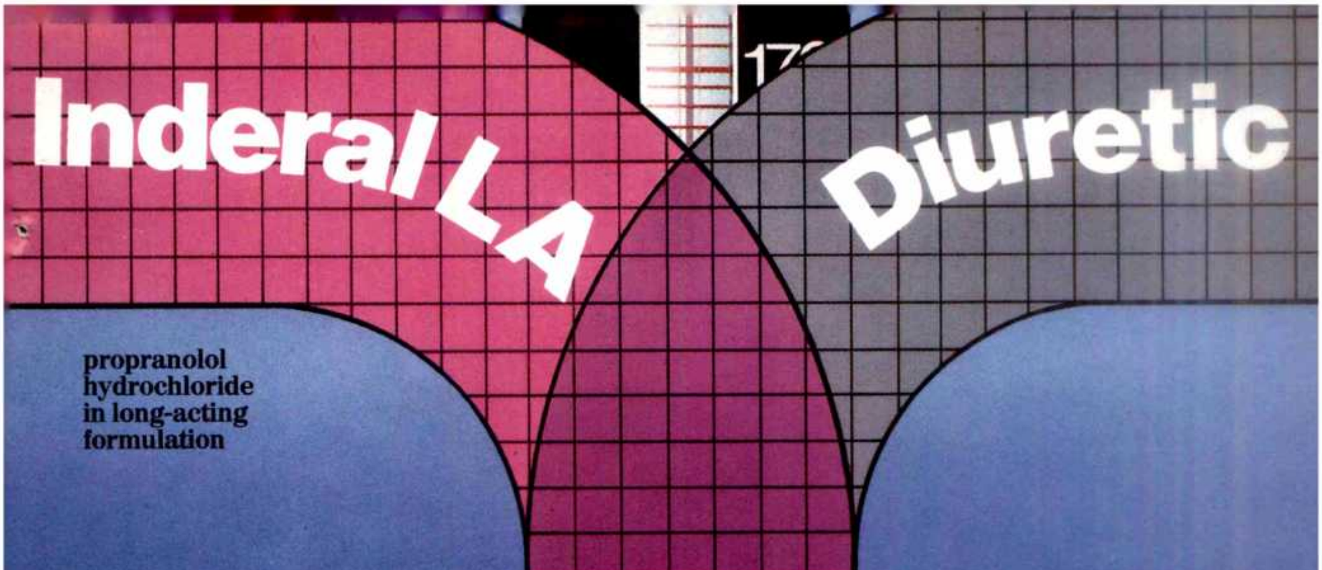

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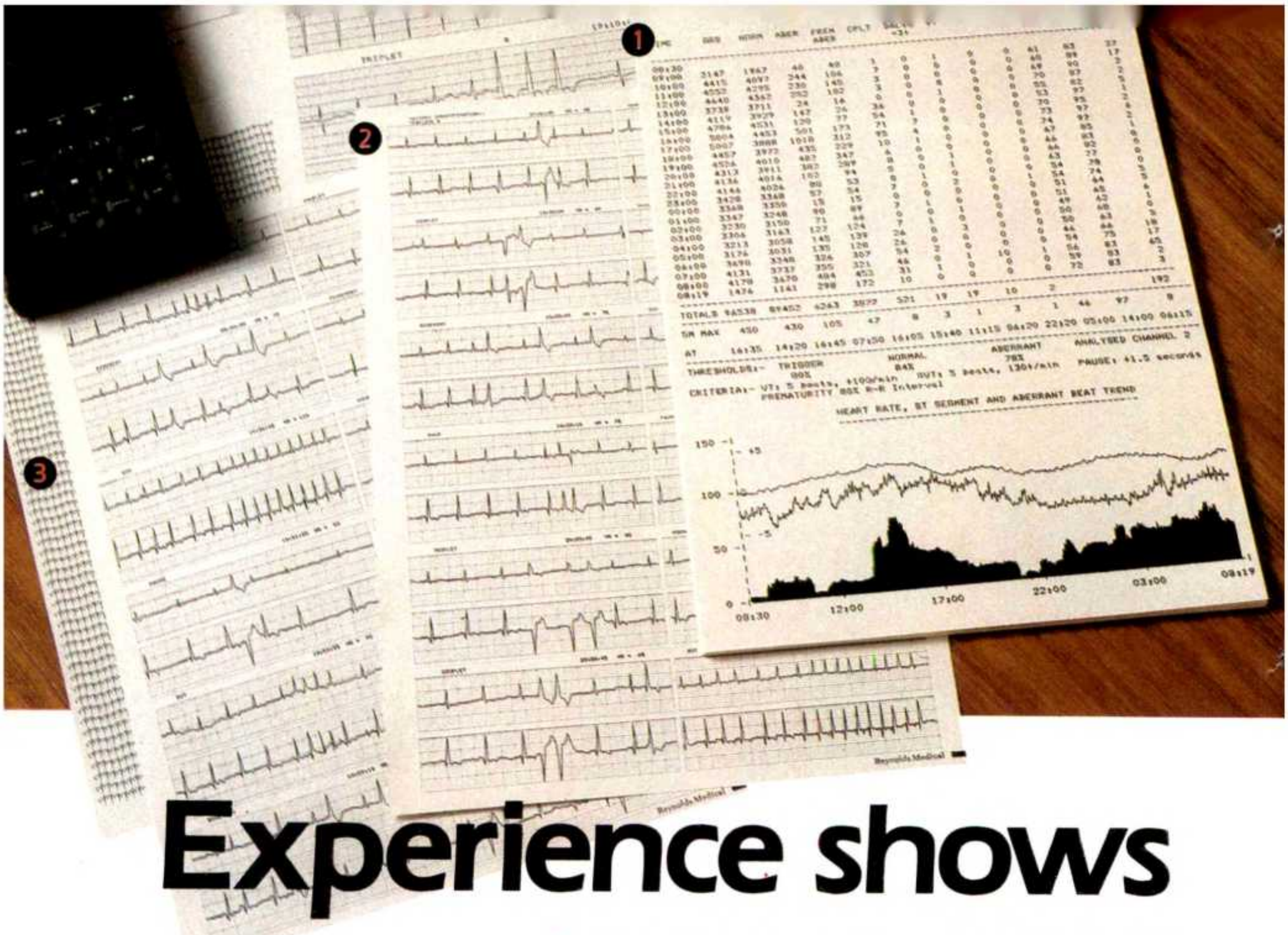

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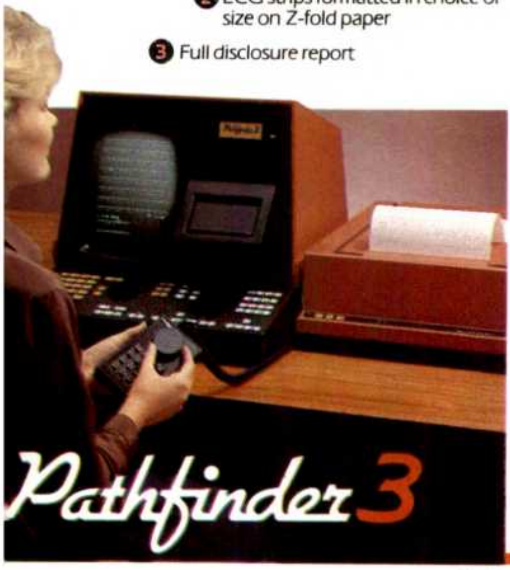

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# Juxtaductal left pulmonary artery obstruction in pulmonary atresia

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SUMMARY The morphology of the central pulmonary artery was studied by selective angiography in 21 previously unoperated patients (aged 11 days–21 years, median 4 years) with pulmonary atresia associated with various types of congenital heart disease. Angiographic findings were confirmed at operation in 10 patients. There was juxtaductal obstruction of the left pulmonary artery in two thirds of the patients with complete atresia in a quarter. Six of seven patients without juxtaductal obstruction had pulmonary valve atresia, but all nine patients with juxtaductal stenosis had truncal atresia. No patient had stenosis of the right pulmonary artery.

Congenital pulmonary atresia often occurs in association with tetralogy of Fallot, atrioventricular discordance, ventriculoarterial discordance, univentricular heart, or with intact ventricular septum.[1 2] Successful correction has been achieved by techniques such as closed or open right ventricular outflow tract reconstruction,[3 4] the Rastelli procedure,[5 6] or the Fontan procedure.[7 8] The presence of normal, or nearly normal, pulmonary arteries is important for successful operation, and peripheral pulmonary stenosis or atresia often make intracardiac repair difficult.[9 10] Preoperative diagnosis of peripheral pulmonary stenosis or atresia by conventional diagnostic methods is not easy. Since 1981 we have used preformed catheters to enable us to visualise the ductus arteriosus and adjacent central pulmonary arteries in patients with pulmonary atresia.[11] We now report the angiographic appearance of the central pulmonary arteries in pulmonary atresia and discuss the development of juxtaductal obstruction of the left pulmonary artery.

## Patients and methods

Since the beginning of November 1981, we have used selective angiography to investigate 77 patients with pulmonary atresia associated with various other congenital anomalies in whom the central pulmonary artery originally gave rise to right and left pulmonary arteries. Twenty one patients who had not been treated surgically form the present study group. They range in age from 11 days to 21 years (median 4 years). Eight are males and 13 are females (Table). All were investigated by cross sectional echocardiography and angiocardiography. The morphology of the central pulmonary artery (pulmonary trunk and main branches) was studied by biplane cut-film or cine angiography. After ventriculography or aortography, selective pulmonary angiography was performed by catheterisation of the persistent ductus arteriosus, except in one patient (case 6) in whom the ductus arteriosus was not patent and in five patients under the age of 1 year (cases 1, 2, 7, 8, and 16). In case 6 the entire central pulmonary artery was visualised by pulmonary vein wedge angiography. In the five infants the central pulmonary artery was clearly visualised by aortography. In six patients (cases 16–21) the proximal left pulmonary artery was atretic and angiography through the ductus arteriosus showed only the distal left pulmonary artery. In three (cases 17, 18, and 20) of these six patients a right pulmonary arteriogram was obtained by injection of contrast medium into the right pulmonary vein wedge position.

Two types of pulmonary atresia were identified on angiograms. In pulmonary valve atresia the pulmonary trunk was long and tubular and sinuses

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Accepted for publication 12 August 1985

Table *Angiographic data on 21 patients with pulmonary atresia*

| *Case No* | *Intracardiac anatomy* | *Age* | *Sex* | *Type of pulmonary atresia* | *PDA* | *Juxtaductal proximal* | *PA obstruction distal* |
|---|---|---|---|---|---|---|---|
| 1 | VAD, VSD | 11 d | M | V | + | – | – |
| 2 | IVS | 12 d | F | V | + | – | – |
| 3 | UVH | 1 yr | F | V | + | – | – |
| 4 | IVS | 3 yr | F | V | + | – | – |
| 5 | AVD, VAD, VSD | 7 yr | F | V | + | – | – |
| 6 | Fallot | 8 yr | M | V | – | – | – |
| 7 | AVSD | 4 mnth | M | T | + | S | S |
| 8 | VAD, VSD | 8 mnth | F | T | + | S | S |
| 9 | Fallot | 1 yr | F | T | + | S | S |
| 10 | VAD, VSD | 2 yr | M | T | + | S | S |
| 11 | UVH | 2 yr | M | T | + | S | S |
| 12 | Fallot | 2 yr | M | T | + | S | S |
| 13 | Fallot | 5 yr | F | T | + | S | S |
| 14 | Fallot | 5 yr | F | T | + | S | S |
| 15 | Fallot | 21 yr | M | T | + | – | – |
| 16 | Fallot | 3 mnth | F | T | + | S | S |
| 17 | AVD, VAD, VSD | 4 yr | F | U | + | A | S |
| 18 | UVH | 6 yr | F | U | + | A | S |
| 19 | Fallot | 9 yr | M | U | + | A | S |
| 20 | Fallot | 10 yr | F | U | + | A | S |
| 21 | Fallot | 10 yr | F | U | + | A | S |

PDA, persistent ductus arteriosus; VAD, ventriculoarterial discordance; VSD, ventricular septal defect; IVS, intact ventricular septum; UVH, univentricular heart; AVD, atrioventricular discordance; AVSD, atrioventricular septal defect; V, valvar; T, truncal; U, unknown; PA, pulmonary artery; +, present; –, absent; S, stenotic; A, atretic.

of Valsalva were seen at its interior end. In truncal atresia the pulmonary trunk was short and cone shaped. These features were most clearly shown on lateral angiograms. In six patients (cases 16–21) with additional juxtaductal pulmonary atresia, the pulmonary trunk could not be visualised. The ductus arteriosus was left sided in 20 patients, including two with the asplenia syndrome (cases 7 and 10). The remaining patient (case 6) had a closed ductus arteriosus.

We use the term juxtaductal obstruction to describe stenosis or atresia of the left pulmonary artery at its junction with the ductus. The diagnosis of postnatal development of juxtaductal atresia was based on the angiographic demonstration, with the catheter in the ductus, of a left pulmonary artery continuous with the ductus, but at an angle to it, absence of major aortopulmonary collateral artery to the right lung, and demonstration of a right pulmonary artery with normal branching pattern by pulmonary vein wedge angiography. Stenosis of the left pulmonary artery was defined as reduction of the internal diameter to less than 50% of its largest diameter. Atresia was diagnosed when no contrast medium passed into the central pulmonary artery despite adequate selective injection into the ductus. In 10 of the 21 patients, the central pulmonary artery was explored at operation after angiographic

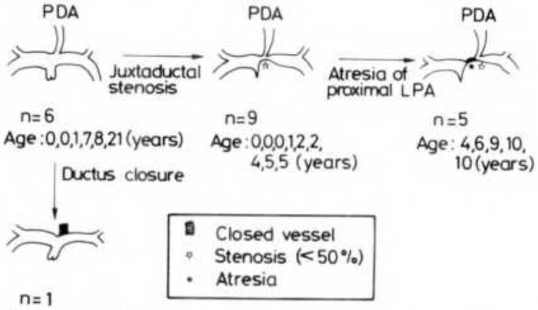

Fig. 1 *Central pulmonary artery patterns in the development of pulmonary atresia associated with congenital heart disease. Numbers of patients and their ages are given.*

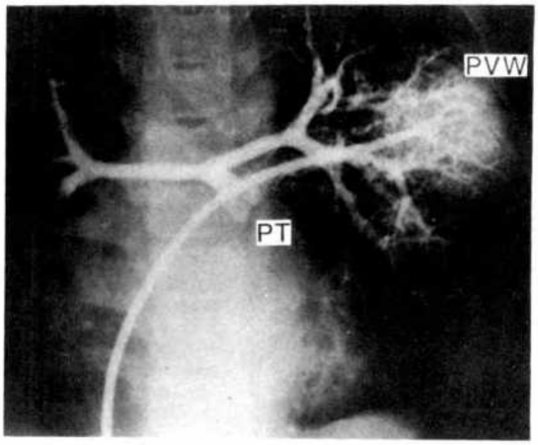

Fig. 2 *Central pulmonary artery visualised by pulmonary vein wedge (PVW) angiography in case 6. An end hole catheter was positioned in the left pulmonary vein via a patent foramen ovale. The ductus was closed. A hypoplastic central pulmonary artery and pulmonary trunk (PT) were visualised. Atresia of the pulmonary valve was diagnosed.*

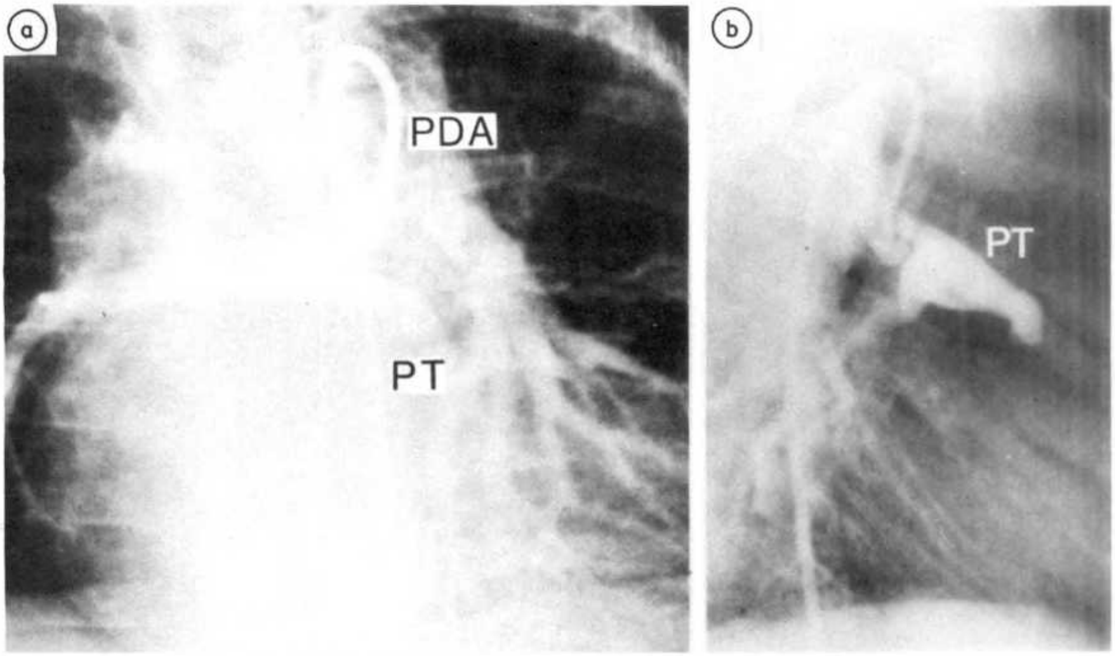

Fig. 3 *(a) Selective angiography of the central pulmonary artery through a preformed ductus catheter in a 2 year old girl with tetralogy of Fallot, pulmonary atresia, persistent ductus arteriosus (PDA), and previous left subclavian to pulmonary artery anastomosis. (b) The pulmonary trunk was small with valve atresia. The left pulmonary artery was visualised only faintly because of wash out from the surgically created shunt. Moderate juxtaductal stenosis was present.*

study; the angiographic diagnosis was confirmed in all.

## Results

### ANGIOGRAMS OF THE PULMONARY ARTERY

The pulmonary trunk was clearly visualised in 16 patients. There was pulmonary valve atresia in six patients (43%) and truncal atresia in the remaining 10 patients.

The appearance of the central pulmonary artery corresponded to one of four patterns (Fig. 1) In seven patients the pulmonary trunk gave rise to right and left branches without stenosis. All these patients except one (case 15) had pulmonary valve atresia. In one (case 6) the ductus was closed, and pulmonary vein wedge angiography showed that the entire central pulmonary artery was hypoplastic (Fig. 2).

In the other 14 patients, there was juxtaductal obstruction of the left pulmonary artery. In nine of these 14 patients the pulmonary trunk divided into right and left pulmonary arteries, but there was a cone shaped narrowing of the left pulmonary artery in each case (Figs. 3, 4, and 5). These nine patients all had truncal atresia. In the remaining five patients, there was complete juxtaductal obstruction, and selective injection of contrast medium into the ductus demonstrated only the left pulmonary artery (Fig. 6). In three of these five patients, pulmonary vein wedge angiography demonstrated normal branching of the right pulmonary artery, though proximal right pulmonary artery and pulmonary trunk were not opacified so that the type of pulmonary atresia could not be determined.

### CORRELATION BETWEEN TYPES OF PULMONARY ATRESIA AND JUXTADUCTAL OBSTRUCTION

Figure 7 shows the age of the patients, the type of pulmonary atresia, and the presence or absence of juxtaductal obstruction. None of the six patients with valvar atresia had juxtaductal obstruction of the left pulmonary artery. In contrast, all except one of those with truncal atresia had juxtaductal obstruction in the left pulmonary artery. Juxtaductal obstruction was more severe proximal than distal to the ductus and five of eight patients aged >3 years with juxtaductal obstruction had atresia.

### ANGIOGRAMS OF THE DUCTUS ARTERIOSUS

The ductus arteriosus was visualised clearly in 20 patients and was catheterised in 15 patients. In 18 patients the lung tubular ductus arose from the

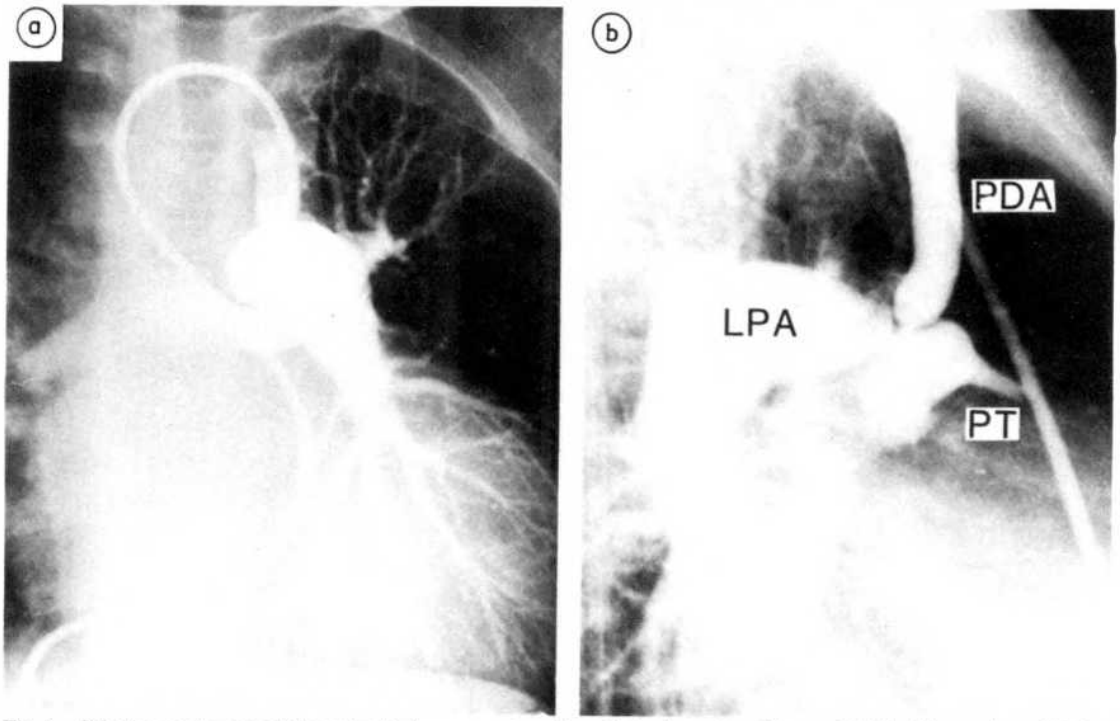

Fig. 4 *Selective angiograms of the central pulmonary artery through the ductus in a 13 year old girl with tetralogy of Fallot, pulmonary atresia, persistent ductus arteriosus, and previous Waterston shunt. (a) The balloon catheter was positioned in the persistent ductus arteriosus (PDA) via right atrium, right ventricle, and ascending aorta. (b) Juxtaductal stenosis and atresia of the pulmonary trunk (PT) were clearly demonstrated. LPA, left pulmonary artery. The right pulmonary artery was not well shown because of wash out from Waterston shunt.*

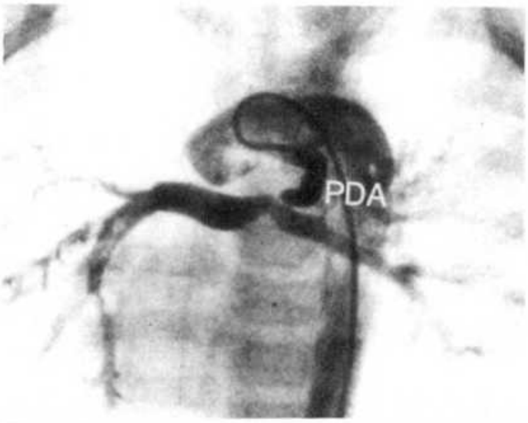

Fig. 5 *Selective angiogram of the central pulmonary artery through the persistent ductus arteriosus (PDA) in case 11, showing cone shaped stenotic ductus and juxtaductal stenosis of the left pulmonary artery. Stenosis of the ductus caused contrast material to be regurgitated into the aorta.*

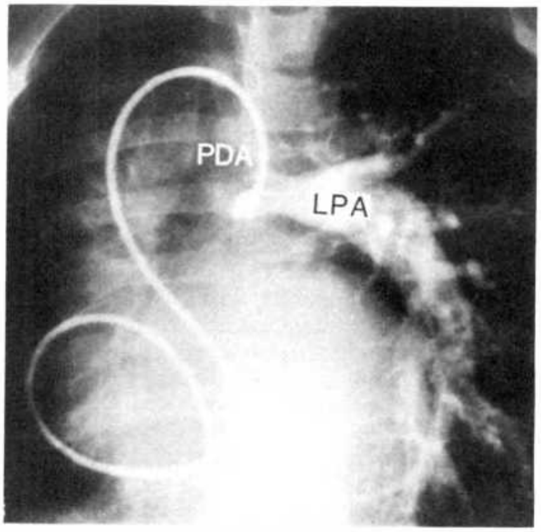

Fig. 6 *Selective angiogram of the central pulmonary artery through the ductus in case 19. The cone shaped left pulmonary artery (LPA) was visualised. The pulmonary artery was atretic proximal to the junction with the persistent ductus arteriosus (PDA). The angiographic balloon catheter was inserted into the ductus through the right ventricle and ascending aorta.*

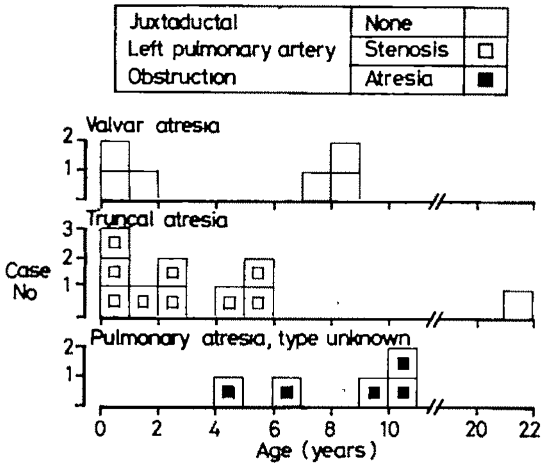

Fig 7 *Types of pulmonary atresia, ages, and juxtaductal obstruction of the left pulmonary artery in patients with pulmonary atresia and no previous operation. Juxtaductal stenosis developed in infancy and early childhood when the pulmonary trunk was atretic. In contrast, patients with atresia of the pulmonary valve did not develop juxtaductal obstruction.*

inferior aspect of the aortic arch with an acute angle between ductus and descending aorta (Fig. 5). In the other two patients, with pulmonary atresia and an intact ventricular septum, the ductus was shorter, originated more caudally at the isthmus, and made an obtuse angle with the descending aorta. The ductus originating from the inferior aspect of the aortic arch was widest at its aortic origin, was tubular or cone shaped, and had localised stenosis at its junction with the pulmonary artery (Figs. 4 and 5). A large ductus could be catheterised with a balloon catheter (Figs. 4 and 6). A small ductus had to be catheterised using a preformed ductus catheter (Figs. 3 and 5).

## Discussion

The development of juxtaductal obstruction of the left pulmonary artery in patients with pulmonary atresia has been described before but not as a definite entity.[12-14] Our angiographic observations provided not only a diagnosis but also information about the development of juxtaductal obstruction.

Several possible mechanisms have been proposed to explain the development of juxtaductal obstruction. It has been suggested that, as in the case of coarctation of the aorta,[15] the shearing force of rapid flow leads to development of a jet lesion at the bifurcation of the artery. This mechanism may explain the progression of juxtaductal obstruction after infancy. We, however, have seen juxtaductal obstruction in a 3 month old infant, and the early appearance of this obstruction suggests that ductal constriction may be a factor. Presbitero *et al* reported evidence to support this hypothesis in one of their patients.[12] They suggested that as the ductus arteriosus closed, ductal tissue extended into and narrowed the left pulmonary artery.

In the nineteenth century it was suggested that ductal tissue might be a cause of coarctation of the aorta (Skodaic theory).[16 17] More recently this Skodaic theory was invoked to account for angiographically diagnosed juxtaductal stenosis in the left pulmonary artery in tetralogy of Fallot in some patients.[18 19]

An understanding of the development of juxtaductal obstruction in pulmonary atresia is relevant to the management of congenital cardiac diseases associated with pulmonary atresia. The present study showed the progressive nature of this lesion, especially proximal to the ductus, and its association with truncal atresia. In patients with truncal atresia, juxtaductal stenosis was already present in infancy—the youngest such patient in this series was 3 months old. After the age of 3 years complete juxtaductal atresia increased in frequency, but the small number of observations precluded quantitative statements about its rate of progression. The present study showed that juxtaductal obstruction developed at both sides of the ductal junction with the left pulmonary artery, but that it progressed more rapidly proximal to the junction. The reason for this is not clear. In contrast, we noticed that juxtaductal obstruction progressed more rapidly distal to the junction after left subclavian-pulmonary artery anastomosis (unpublished data). We believe that juxtaductal obstruction may progress more rapidly where blood flow is more turbulent.

It is remarkable that in this study juxtaductal obstruction was an almost invariable finding in patients with truncal atresia but did not occur in those with valvar atresia. This difference is less clear cut in our continuing study of peripheral pulmonary artery stenosis in pulmonary atresia after palliative operation. There are several possible explanations of the association of juxtaductal obstruction with truncal atresia. There is evidence that pulmonary valve atresia, especially when associated with intact ventricular septum, develops later in fetal life than truncal atresia.[20] This may in turn, lead to differences in development of the juxtaductal portion of the pulmonary artery. Specifically, the size of the pulmonary artery or the distribution of the ductal tissue in the left pulmonary artery may be different in these two types of pulmonary atresia. This remains to be studied.

A few comments are needed on the technique of selective angiography of the pulmonary artery in patients with pulmonary atresia and a central pulmonary artery. The origin and shape of the ductus arteriosus in pulmonary atresia are characteristic.[14 20] It arises from the inferior aspect of the aortic arch and makes an acute angle with the descending aorta. We have used three techniques for catheterisation of this type of ductus. In a large high flow ductus, a transvenous balloon catheter (Berman) can be advanced through the right ventricle and ascending aorta into the ductus. An angiographic catheter may also be inserted through the brachial artery. In 1981 we developed a third technique in which we used a preformed ductus catheter.[11] This catheter is inserted percutaneously from the femoral artery and easily enters the ductus. We have used it extensively in children aged >1 year, and even a narrow ductus with an internal diameter of 2 mm can be entered.

We are indebted to Dr Leonard M Linde, Clinical Professor of Pediatric Cardiology, University of Southern California School of Medicine, and Miss Miyuki Kahn for their help.

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# An echocardiographic study of perimembranous ventricular septal defect with left ventricular to right atrial shunting

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SUMMARY Twenty nine patients with isolated perimembranous ventricular septal defects were investigated by M mode, cross sectional, and pulsed Doppler echocardiography. Tricuspid valve anomalies were present in all six patients with a left ventricular-right atrial shunt but in only six (26%) of 23 patients who had interventricular shunts only. Systolic flutter of the tricuspid valve was shown in five (83%) of the six patients with a ventriculoatrial shunt but not in the other patients. Systolic turbulence in both the right ventricle and right atrium was detected by Doppler echocardiography only in patients with ventriculoatrial shunting. A perimembranous ventricular septal defect with left ventricular to right atrial shunt can be diagnosed by its combined M mode, cross sectional, and pulsed Doppler echocardiographic features.

A left ventricular to right atrial shunt is usually not recognised until cardiac catheterisation has been performed. An increase in atrial oxygen saturation when the interatrial septum is intact suggests such a communication. The passage of contrast medium across the ventricular septum with immediate opacification of the dilated right atrium during selective left ventriculography is diagnostic.[1] Some of the echocardiographic features of ventriculoatrial communications have been described in single case reports.[2-7] The present study is an attempt to define the M mode, cross sectional, and pulsed Doppler echocardiographic features of perimembranous ventricular septal defects with left ventricular to right atrial shunts.

## Patients and methods

Twenty nine patients with isolated perimembranous ventricular septal defects were studied. Six patients (aged 2 months to 26 years (mean 8 years 1 month)) had both interventricular and ventriculoatrial shunts. Twenty three patients (aged 3 months to 26 years (mean 4 years 9 months)) had interventricular shunts only. In all patients cardiac catheterisation and cinecardioangiographic examination confirmed these intracardiac anomalies. Echocardiography was performed using the duplex system of the Mark V ATL instrument (MK 600) (Advanced Technology Laboratory, Bellevue, WA 98008) fitted with either a 3 or 5 MHz transducer. Standard views were used to identify the septal defect[8] and to determine its relation to the tricuspid valve. The presence of tricuspid valve anomalies and M mode echocardiography of the tricuspid valve were recorded.

Left to right shunting in the right ventricle close to the ventricular septal defect, the possibility of tricuspid regurgitation, and direct ventriculoatrial shunting were evaluated by pulsed Doppler echocardiography. The sample volume was initially placed in the right ventricle adjacent to the septal defect and then in the right atrium close to the tricuspid valve. Any Doppler frequency shift indicating turbulent flow was noted. The direction and flow pattern of laminar or disturbed blood flow were displayed graphically. (Aliasing occurred when the turbulent flow exceeded the Nyquist limit of the machine.) Audio signals were also used to assist in the differentiation between laminar and turbulent flow. Simultaneous M mode display was used to determine the position of the sample volume and the elec-

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Accepted for publication 20 August 1985

Table 1 *Summary of echocardiographic, cardiac catheterisation, and cineangiographic findings in patients with ventriculoatrial shunt*

| *Case* | *Sex/age* | *VSD* | *Tricuspid valve anomalies* | *Tricuspid valve flutter* | *Systolic turbulence* | | *Catheterisation findings* | | *LV angiogram findings* |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | *RA* | *RV* | *PA pressure (mm Hg)* | *QP:QS* | |
| 1 | F/5½ yr | Perimembranous | Adherence of septal leaflet to VSD margins | + +, systolic | + | + | 37/6 (mean 26) | 1·4:1 | Contrast to both RA and RV |
| 2 | M/2 month | Perimembranous | Widened anteromedial commissure (thickened, dysplastic valve at necropsy) | 0 | + | + | 55/25 (mean 30) | 3·9:1 | Contrast to RA |
| 3 | M/9 yr | Not seen | Thickened septal leaflet | + +, systolic | + | + | 32/11 (mean 20) | 1·7:1 | Small jet to both RA and RV |
| 4 | F/7 yr | Perimembranous | Adherence of septal leaflet to VSD margins | + +, systolic | + | + | 32/10 (mean 20) | 2·3:1 | Contrast to both RA and RV |
| 5 | F/10 month | Perimembranous | Pouch like malformation of septal leaflet | +, systolic | + | + | 24/14 (mean 18) | 2·5:1 | "Aneurysm of membranous septum". Contrast to both RA and RV |
| 6 | F/26 yr | Perimembranous | Pouch like malformation of septal leaflet | +, systolic | + | + | 30/6 (mean 16) | 2:1 | "Aneurysm of membranous septum". Contrast to both RA and RV |

LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle; QP:QS, ratio of pulmonary blood flow to systemic blood flow; VSD, ventricular septal defect.

trocardiogram was used to time the events. When the defect was not clearly visualised, a search was made for systolic turbulence in different parts of the right ventricle by varying the position of the sample volume. Detection of systolic spectral dispersion in the right atrium or ventricle by Doppler technique was accepted as evidence of shunting.

## Results

Table 1 gives the findings in the patients with ventriculoatrial shunting, and Table 2 compares the findings in the two groups.

### VENTRICULOATRIAL SHUNTING

The septal defect was visualised in five of the six patients. Tricuspid valve anomalies were observed in all six patients. A redundant septal leaflet with a pouch like malformation in the vicinity of the septal defect (Fig. 1a) was observed in two patients. Adherence of valve tissue to the margins of the septal defect (Fig. 1b and c) was demonstrated in two other patients. Widening of the anteromedial commissure (Fig. 2b and c) was seen in one other patient. In the remaining patient, there was thickening and distortion of the septal leaflet. Systolic flutter of the tricuspid valve leaflet (Fig. 3) was seen in the M mode echocardiograms of five patients. Doppler echocardiography showed systolic turbulence in both right ventricle and right atrium (Fig. 4) in all six patients.

Table 2 *A comparison of the echocardiographic features of patients with or without a ventricular shunt*

| *Feature* | *No of patients* | |
|---|---|---|
| | *With shunt (n = 6)* | *Without shunt (n = 23)* |
| VSD visualised by cross sectional echocardiography | 5 | 17 |
| Presence of tricuspid valve anomalies | 6 | 6 |
| Presence of tricuspid valve systolic flutter | 5 | 0 |
| Systolic turbulence detected by Doppler in right atrium | 6 | 0 |
| Systolic turbulence detected by Doppler in right ventricle | 6 | 23 |

### INTERVENTRICULAR SHUNT ALONE

A septal defect was visualised in 17 (74%) of the 23 patients. Twelve of the defects mainly affected the inlet septum and the remaining five extended to the apical trabecular and outlet region. In two patients, the subcostal four chamber view gave a false impression that the defect extended above the tricuspid valve annulus (a direct ventriculoatrial communication (Fig. 5a)). This was excluded by readjusting the transducer position (Fig. 5b) and by Doppler echocardiography (Fig. 5c). An anomaly of the tricuspid valve was demonstrated in six patients (26%). Pouch like malformations with redundancy of the septal leaflet were seen in three patients (Fig. 5b) and adherence of accessory valve tissue to the margins of the defect was seen in the other three. There was no abnormal oscillation of the tricuspid valve in any patient. In all 23 patients Doppler techniques showed systolic turbulence in the right ventricle alone (Fig. 5c).

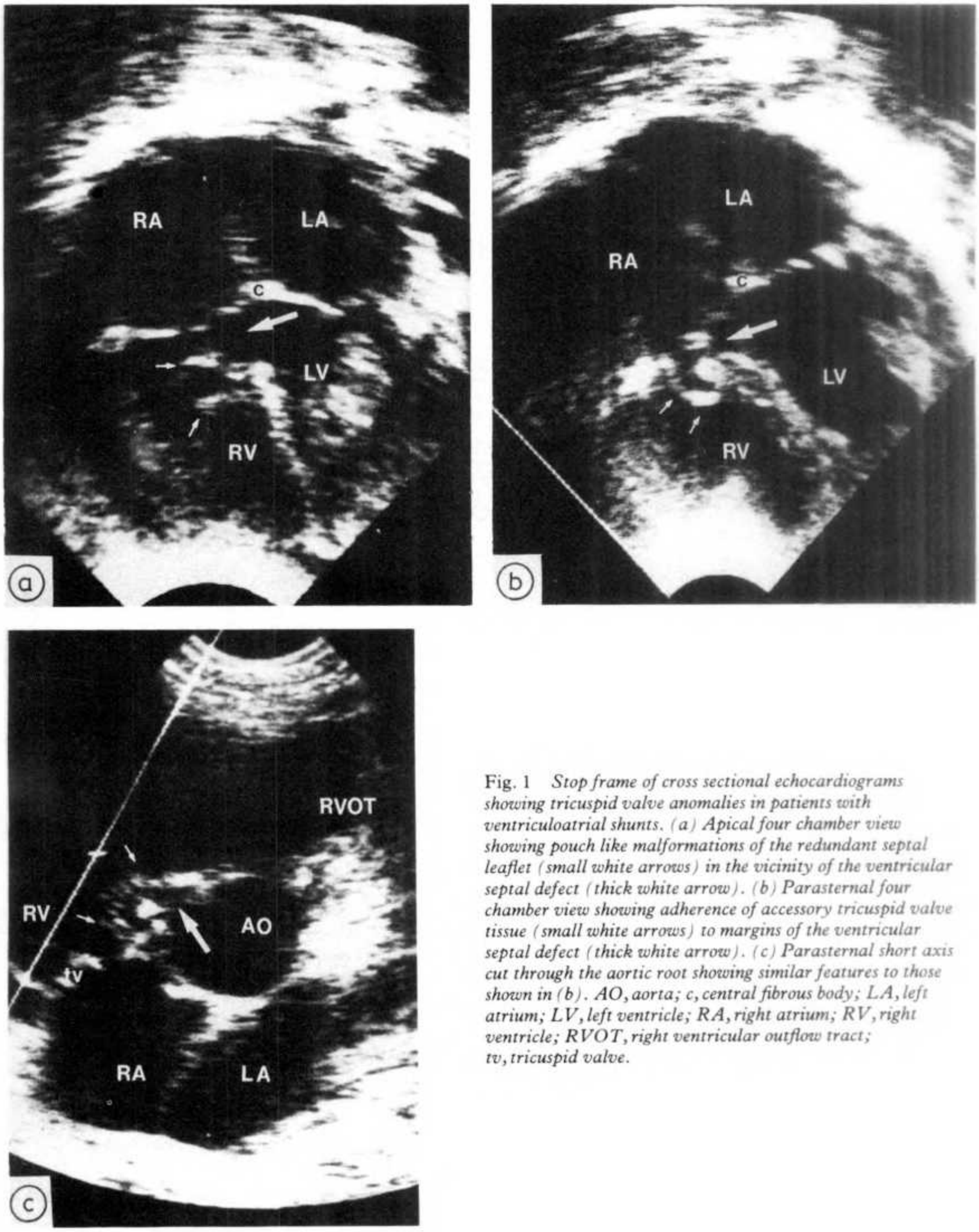

Fig. 1 *Stop frame of cross sectional echocardiograms showing tricuspid valve anomalies in patients with ventriculoatrial shunts. (a) Apical four chamber view showing pouch like malformations of the redundant septal leaflet (small white arrows) in the vicinity of the ventricular septal defect (thick white arrow). (b) Parasternal four chamber view showing adherence of accessory tricuspid valve tissue (small white arrows) to margins of the ventricular septal defect (thick white arrow). (c) Parasternal short axis cut through the aortic root showing similar features to those shown in (b). AO, aorta; c, central fibrous body; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; RVOT, right ventricular outflow tract; tv, tricuspid valve.*

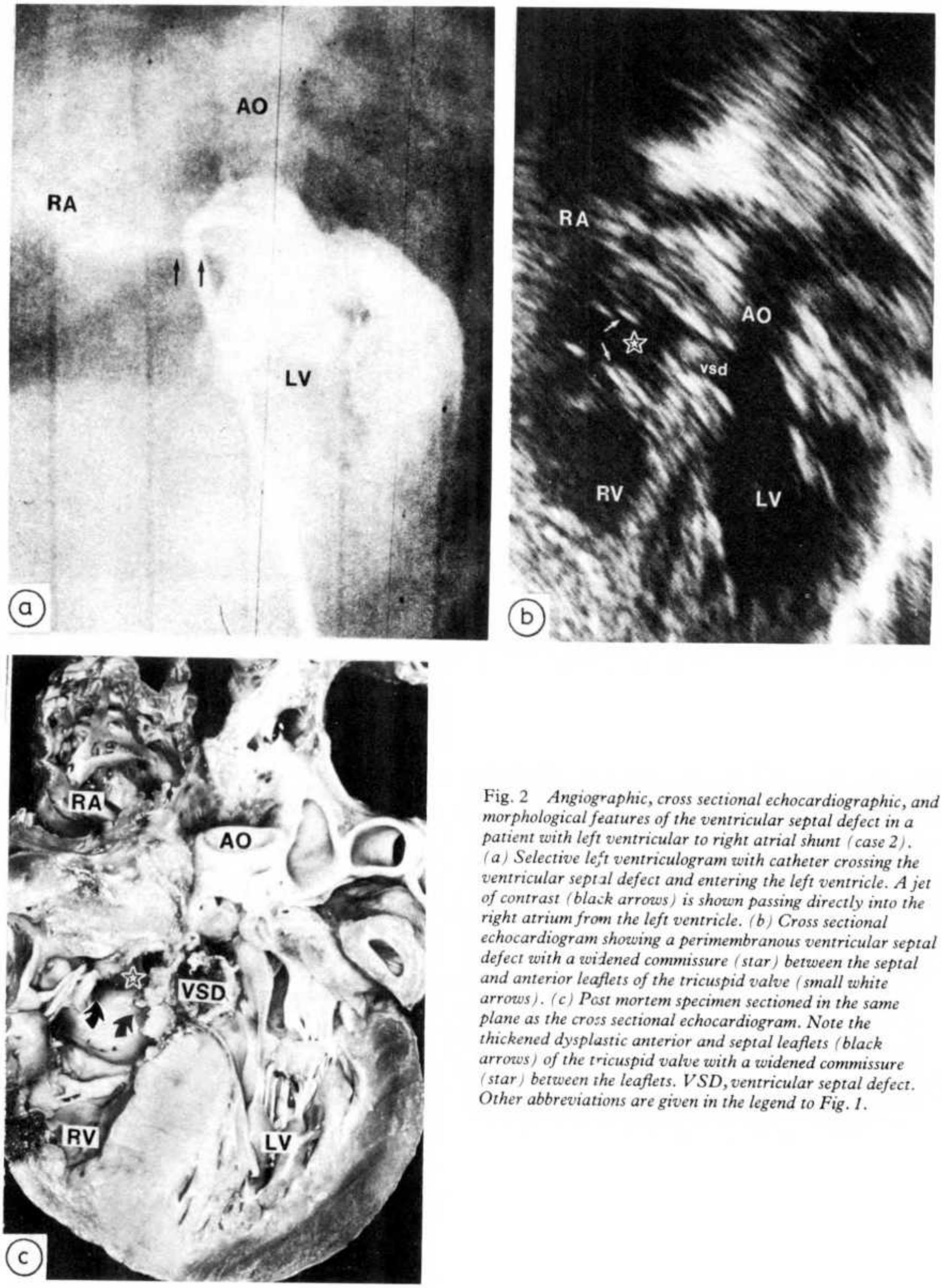

Fig. 2 *Angiographic, cross sectional echocardiographic, and morphological features of the ventricular septal defect in a patient with left ventricular to right atrial shunt (case 2). (a) Selective left ventriculogram with catheter crossing the ventricular septal defect and entering the left ventricle. A jet of contrast (black arrows) is shown passing directly into the right atrium from the left ventricle. (b) Cross sectional echocardiogram showing a perimembranous ventricular septal defect with a widened commissure (star) between the septal and anterior leaflets of the tricuspid valve (small white arrows). (c) Post mortem specimen sectioned in the same plane as the cross sectional echocardiogram. Note the thickened dysplastic anterior and septal leaflets (black arrows) of the tricuspid valve with a widened commissure (star) between the leaflets. VSD, ventricular septal defect. Other abbreviations are given in the legend to Fig. 1.*

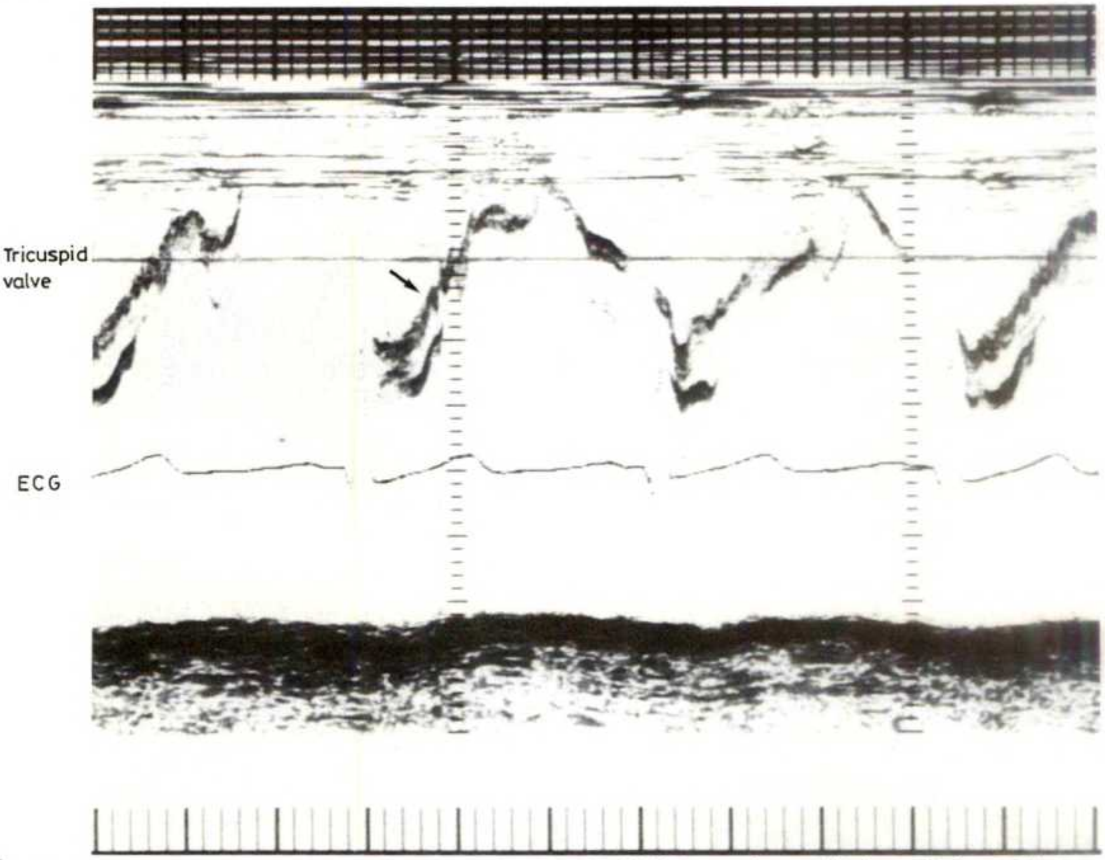

Fig. 3 *M mode echocardiography of the tricuspid valve showing the high frequency low amplitude systolic flutter (black arrow). ECG, electrocardiogram.*

## Discussion

Ventriculoatrial communications are divided into two main groups depending upon whether the septal defect is above or below the level of attachment of the septal leaflet of the tricuspid valve. Occasionally both supravalvar and infravalvar areas are affected.[1] The cases available for study had the most common type of shunt, namely that associated with a perimembranous ventricular septal defect.

There was no difference in the cross sectional echocardiographic appearance of the defect in the two groups of patients. In some patients with an exclusively ventricular shunt, tilting the transducer slightly more anteriorly than usual in the subcostal four chamber view produced a false image of ventriculoatrial communication. When the transducer is not properly positioned in a patient in whom the tricuspid valve tissue is adherent to the margin of the ventricular septal defect, the upper part of the defect may appear to lie above the level of attachment of the tricuspid valve (Fig. 5a). This impression can be easily corrected by adjustment of the position of the transducer so that the plane passes through the central fibrous body of the heart in the apical four chamber view (Fig. 5b). The absence of a ventriculoatrial shunt can also be confirmed by the lack of systolic turbulence in the right atrium (Fig. 5c).

It is generally accepted that infravalvar ventriculoatrial communications always have associated anomalies of the tricuspid valve adjacent to the defect.[9-11] The following tricuspid valve anomalies had been identified and described[1 9 10 12-17]: clefts or perforations of the septal leaflet; thickening and distortion of the septal leaflet; adherence of valve tissue to the margins of the defect; pouch like malformation caused by the presence of redundant valve tissue, and finally widening of, or incomplete attachment of, the tricuspid valve to the membranous component of the ventricular septum at the antero-

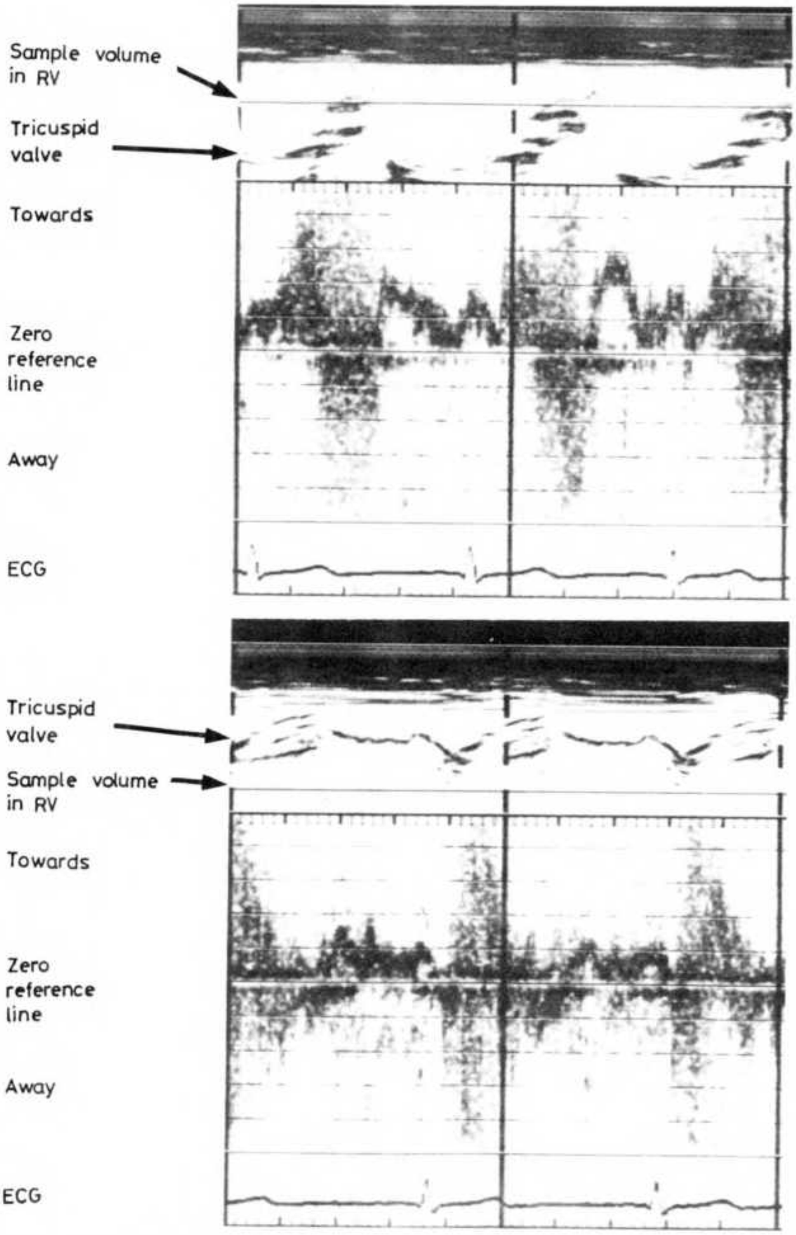

Fig. 4 *Graphic display of Doppler echocardiography showing systolic turbulence in both right ventricle (RV) and right atrium (RA). ECG, electrocardiogram.*

medial commissure. Some of these anomalies are probably important in the pathogenesis of the shunt while others may only be associated anomalies. Some of these anomalies were demonstrated echographically in all patients with a ventriculoatrial shunt and in a quarter of those without. The importance of these anomalies could not be determined echocardiographically. The pouch like mal-

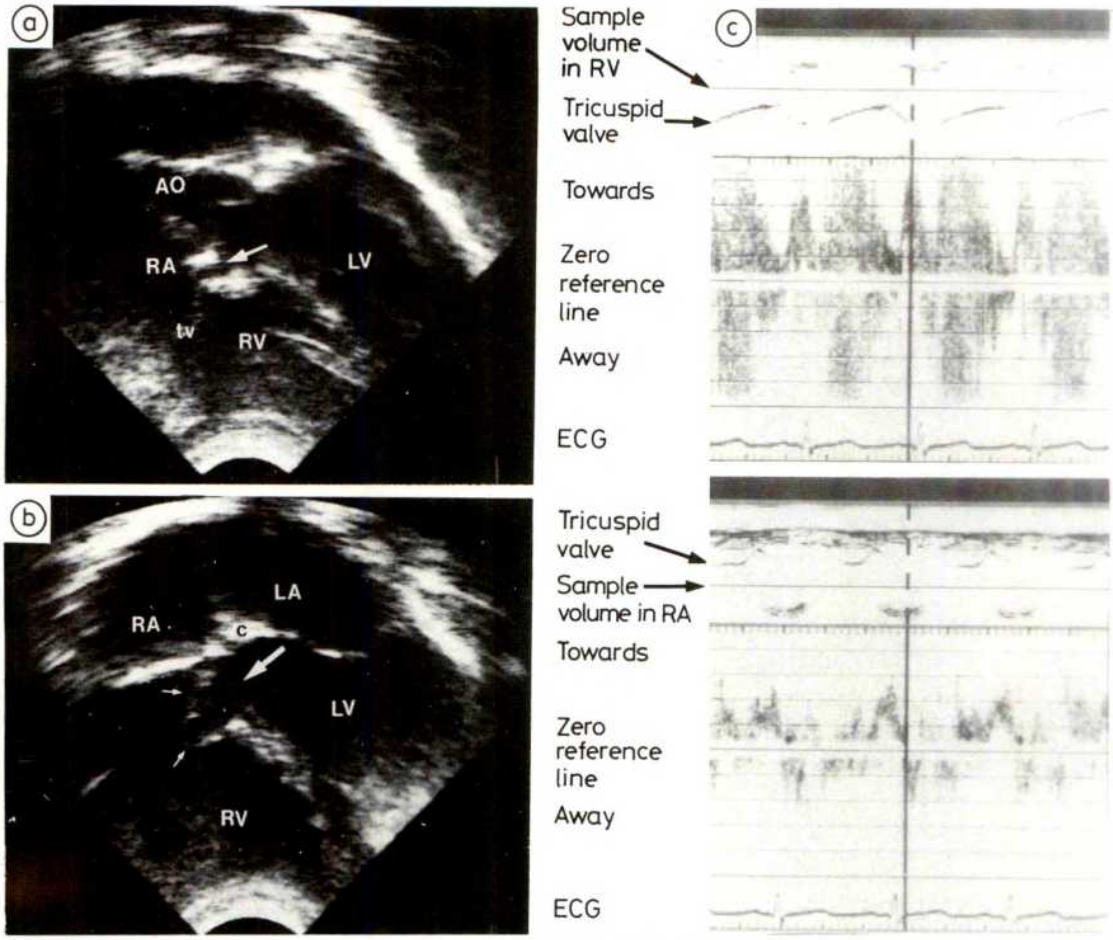

Fig. 5 *(a) Malaligned subcostal four chamber view of cross sectional echocardiogram in two patients with interventricular shunts alone. This view gave a false impression of direct communication (white arrow) between the left ventricle and right atrium. (b) Apical four chamber view passing through the central fibrous body showing a perimembranous ventricular septal defect (thick white arrow) with pouch like malformation of redundant septal leaflet of the tricuspid valve (small white arrows). (c) Graphic display of Doppler echocardiogram showing systolic turbulence in the right ventricle but not in the right atrium. ECG, electrocardiogram. Other abbreviations are given in the legend to Fig. 1.*

formation of the tricuspid septal leaflet seen by angiography resembles the so called aneurysm of the membranous septum.[18] It may represent one of the features of the normal variations in tricuspid valve attachments to the membranous component of the ventricular septum.[11] The adherence of tricuspid valve tissue to the margins of the defect may represent a mechanism of spontaneous closure.[15 18] The tricuspid anomalies by themselves are not diagnostic of a ventriculoatrial shunt. When they are demonstrated in the presence of a perimembranous defect, however, an associated ventriculoatrial shunt should be suspected. Systolic turbulence should be sought in the right atrium in the vicinity of the anomaly.

The rare echocardiographic finding of systolic flutter of the tricuspid valve was of diagnostic value in cases of congenital infravalvar ventriculoatrial communication[2 3] The flutter was of high frequency and low amplitude. Grenadier *et al*, however, reported low frequency high amplitude oscillations of the tricuspid valve throughout systole in a 13 year old girl with an infravalvar ventriculoatrial communication and mitral regurgitation.[5] In the present study, high frequency low amplitude systolic flutter of the tricuspid valve was demonstrated in five of the six patients with a ventriculoatrial shunt. It seems reasonable to suggest that the low frequency high amplitude tricuspid oscillations reported by Grenadier and associates are a variant when there is associated mitral regurgitation. The only patient (case 2) who did not have tricuspid flutter died. This infant died of fungal septicaemia eight weeks after closure of the septal defect. Necropsy showed a rather rigid and dysplastic tricuspid valve (Fig. 2c). This accords with the hypothesis of Nanda *et al* that one of the requirements for systolic flutter of the tricuspid valve is sufficient local flexibility.[2]

The Doppler echocardiographic demonstration of systolic turbulence in both right ventricle and right atrium confirms that shunting occurs at both ventricular and atrial levels when there is left ventricular to right atrial communication. In the present study we found several distinct echocardiographic features in patients with isolated perimembranous ventricular septal defect and an infravalvar ventriculoatrial shunt. First, systolic flutter of the tricuspid valve was present in most patients. Secondly, anomalies of the tricuspid septal leaflet and systolic turbulence, as detected by Doppler echocardiography, were invariably present in both right ventricle and right atrium.

We thank Professor R H Anderson for his invaluable advice and assistance.

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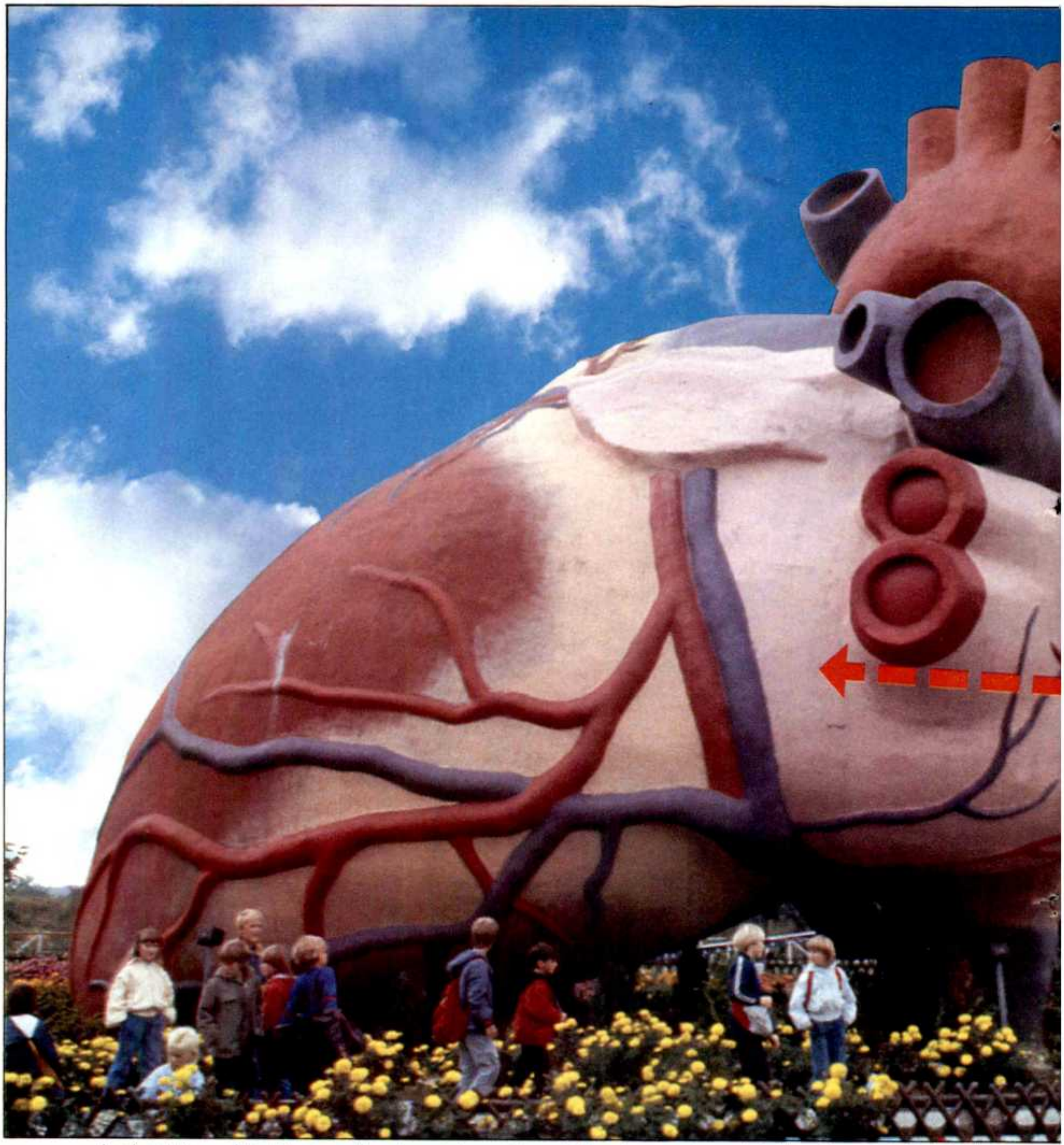

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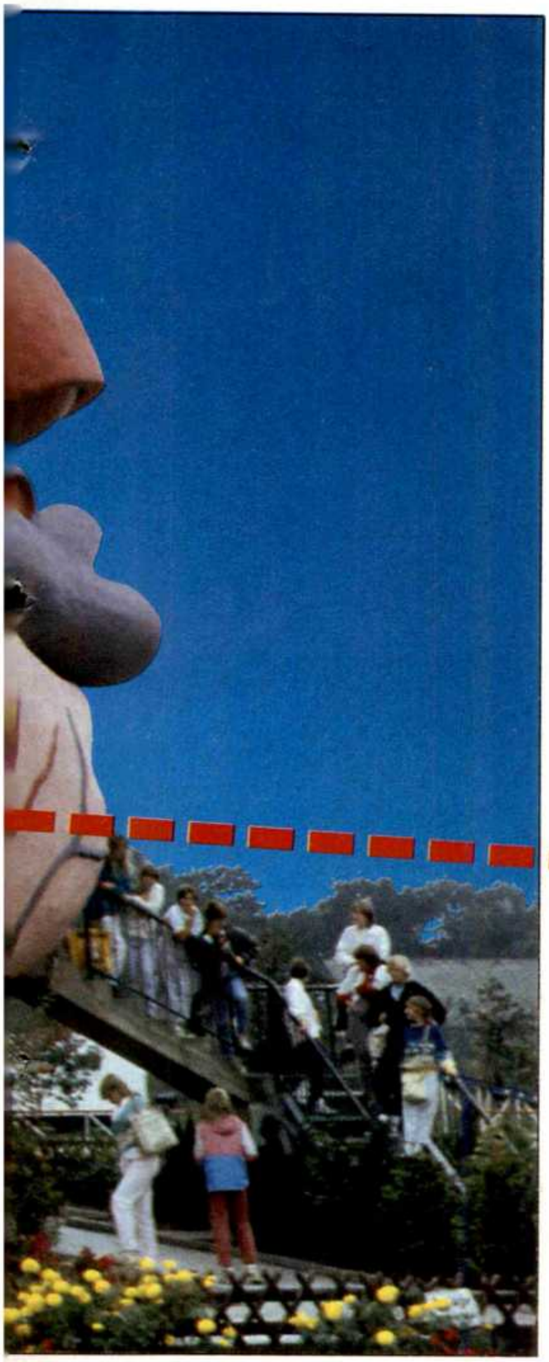

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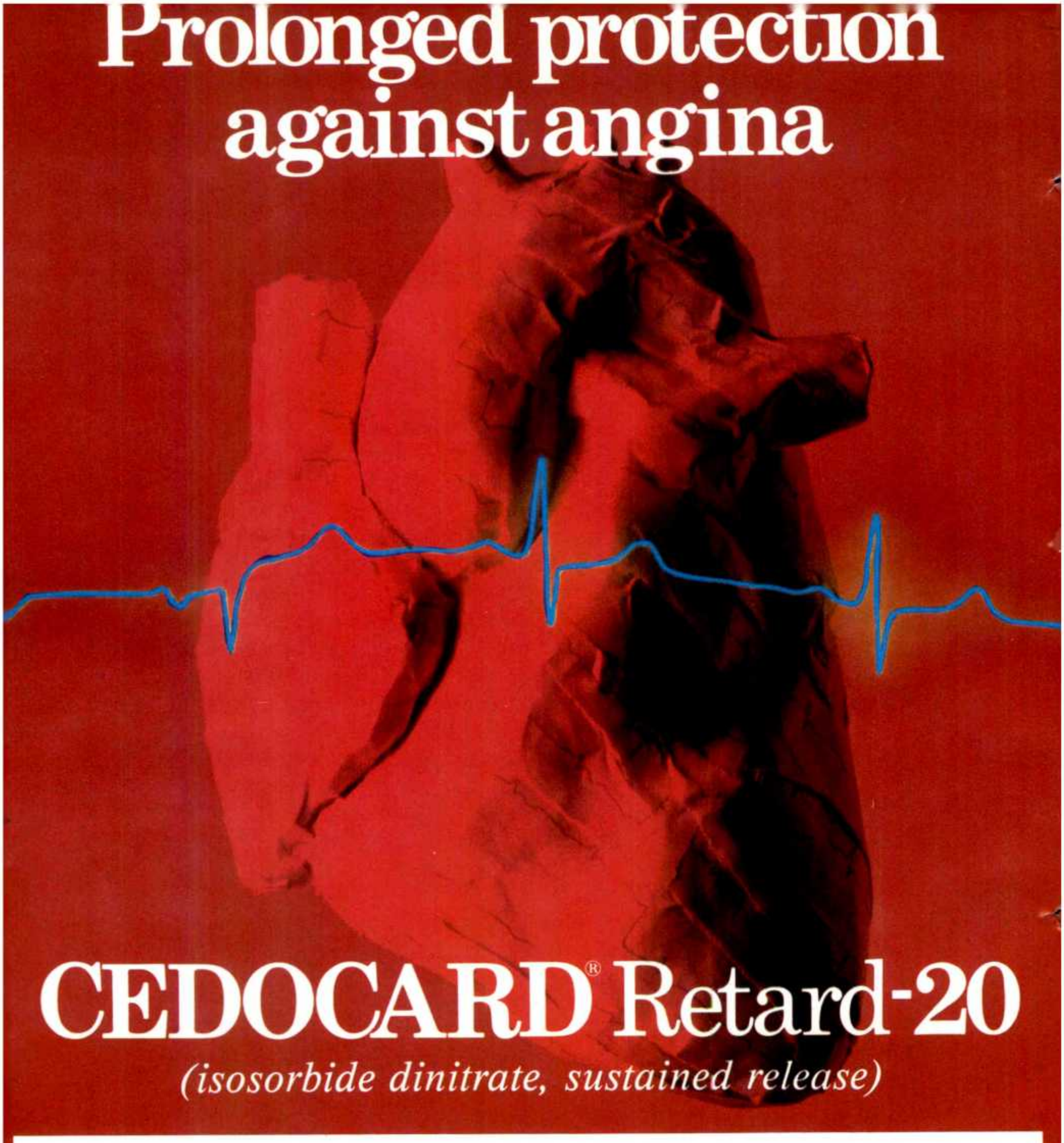
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# Increased vagal tone as an isolated finding in patients undergoing electrophysiological testing for recurrent syncope: response to long term anticholinergic agents

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SUMMARY Features suggestive of an isolated increase in vagal tone during electrophysiological study were found in 12 patients with recurrent near syncope or syncope. Results at neurological and cardiac evaluation were otherwise normal. The increased tone or heightened sensitivity to vagal tone was manifested by abnormal atrioventricular nodal refractoriness and conduction that were reversed with atropine. The patients underwent long term treatment with an anticholinergic agent (propantheline bromide) and 75% improved. Before treatment they had experienced a median of seven episodes (range 3–28) of near syncope or syncope during 10·5 months (range 1–60). During treatment these episodes decreased to a median of one (range 0–15) during 22·5 months (range 3–67); six patients experienced no further symptoms. Three patients continued to have syncope while on treatment, and one of these required permanent cardiac pacing. No additional cause for syncope was identified in any patient.

During electrophysiological assessment of patients with syncope, evidence may be obtained pointing to an increase in vagal tone. In many of these patients treatment with anticholinergic drugs seemed to improve or eliminate the symptoms.

There have been isolated case reports of syncope being caused by excessive vagal tone in people who are otherwise healthy. In some situations if syncope occurs without the typical warning symptoms the individual may be at considerable risk.[1-3]

Abnormal atrioventricular nodal function is a prominent electrophysiological phenomenon that is demonstrated both during spontaneous vasovagal episodes and during electrophysiological testing in patients who have a clinical history suggestive of vasovagal syncope but who are symptom free at the time of study.[1 3-5] Increased vagal tone, however, may also be induced by the stress of the electrophysiological study in patients with no history of near syncope or syncope.

We have assumed that clinical episodes of near syncope or syncope in patients in whom the only identifiable abnormality is increased vagal tone during electrophysiological study were the result of the increased vagal tone. We have attempted to control the symptoms with specific anticholinergic treatment aimed at reversing the increased vagal tone. We report the long term results of this treatment in 12 patients with near syncope or syncope and isolated increased vagal tone at electrophysiological study.

## Patients and methods

*Patients*—Twelve patients (five male and seven female) were identified who presented with recurrent near syncope or syncope; their only identifiable abnormality was increased vagal tone (defined below) at the time of electrophysiological study. Their mean age was 48 years (range 15–84 years). None of the

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Accepted for publication 24 September 1985

patients had an identifiable cause for their symptoms despite neurological (including electroencephalography and computed tomography when indicated) and cardiac examinations (including extensive ambulatory monitoring). Associated cardiac disease included partial anomalous pulmonary venous drainage with a non-significant shunt in one patient and stable coronary artery disease in two patients. Patients were excluded from the study if they had any cardiac abnormalities that could be a cause of near syncope or syncope, including carotid sinus hypersensitivity, important postural hypotension (a decrease in systolic pressure of more than 20 mm Hg on standing), and important neurological disease.

*History of syncope*—The patients were referred for evaluation of multiple episodes of syncope or near syncope that were causing considerable disruption to daily activities. One patient had been injured during a syncopal episode, and four other patients had experienced symptoms in situations in which their life was threatened. There was no prodrome suggestive of a vasovagal event in five of the 12 patients; all of these patients had syncope without warning. Only three patients gave a history of vasovagal events in response to painful or emotional stimuli. In eight of the patients with symptoms, syncope or near syncope was more frequent when they were standing, although three of these patients also experienced symptoms while they were sitting or lying. Four patients did not describe any specific precipitating or aggravating factors. Two patients exercised regularly, but they were not highly trained athletes.

*Electrocardiographic monitoring*—None of the patients had evidence suggestive of increased vagal tone on their 12 lead electrocardiogram (heart rate <55 beats per minute or atrioventricular conduction delay). Asymptomatic Wenckebach periodicity was noted in two patients during 24 hour monitoring.

*Definition of increased vagal tone*—Increased vagal tone at the time of electrophysiological study was defined as (*a*) atrioventricular nodal Wenckebach periodicity occurring at atrial paced rates of ⩽120 beats per minute, (*b*) abnormally prolonged atrioventricular nodal functional and effective refractory periods (>502 ms and >374 ms, respectively),[6,7] with restoration of a normal interval after the intravenous injection of atropine (2·4 mg).

*Electrophysiological study*—The electrophysiological study was performed as previously described.[8] Antiarrhythmic agents were discontinued at least five drug half lives before evaluation. Two or three electrode catheters were introduced via the right femoral vein and positioned in the high right atrium, the atrioventricular junction, and the right ventricular apex. Atrial pacing was performed for 30 seconds at incremental rates starting just faster than sinus rhythm and increasing up to 200 beats per minute. Atrial extrastimuli were then introduced, and the R–R interval was scanned during sinus rhythm and during atrial pacing. Heart rate and blood pressure were monitored during right carotid sinus massage and then during left carotid sinus massage. After this ventricular pacing was performed with incremental ventricular pacing for five beats until 2:1 capture or a paced cycle length of 200 ms was attained. This was followed by single and double extrastimuli, and the R–R interval was scanned during sinus rhythm and ventricular pacing at 100 and 150 beats per minute from the right ventricular apex and outflow tract. The study was then repeated (without ventricular stimulation) after intravenous atropine (2·4 mg).

*Long term follow up and anticholinergic treatment*—All patients were followed up directly as outpatients or by telephone contact. During long term follow up no other cause for the symptoms was identified. The patients were treated with propantheline bromide (7·5 to 15 mg three or four times daily) and the dose was adjusted to eliminate side effects. We did not believe that a placebo trial was ethical in this group of patients with profound potentially life threatening syncope.

We used Student's *t* test for paired data for statistical analysis of the electrophysiological results. Corrected sinus node recovery time was obtained by subtracting the basic cycle length from the sinus node recovery time. The effective refractory period of the atrioventricular node was defined as the longest $A_1A_2$ measured with the His bundle electrogram that failed to conduct to the His bundle. The functional refractory period of the atrioventricular node was defined as the shortest $H_1H_2$ interval in

Table 1 *Electrophysiological variables (mean (SD)) before and after atropine in patients with recurrent syncope*

| *Variable* | *Baseline* | *After atropine* | *p* |
|---|---|---|---|
| Heart rate (beats/min) | 62 (9) | 96 (16) | 0·001 |
| Corrected sinus node recovery time (ms) | 345 (167) | 189 (69) | NS |
| Atrial pacing rate (beats/min) resulting in | | | |
| AV node Wenckebach | 99 (15) | 165 (20) | 0·001 |
| AV node FRP (ms) | 616 (67) | 408 (49) | 0·001 |
| AV node ERP (ms) | 480 (72) | 295 (37) | 0·001 |

AV, atrioventricular, ERP, effective refractory period; FRP, functional refractory period, NS, not significant.

response to any $A_1A_2$ interval.

## Results

*Electrophysiological findings*—Table 1 summarises the results of electrophysiological testing before and after the administration of atropine. All abnormalities of increased vagal tone (sinus rate and atrioventricular nodal conduction and refractoriness) became normal on atropine. One patient had an abnormally prolonged corrected sinus node recovery time (> 525 ms) that became normal after the administration of atropine. There were no abnormalities of His-Purkinje function or inducible ventricular arrhythmias.

*Anticholinergic treatment and long term follow up*—All patients received anticholinergic treatment with propantheline bromide. Before anticholinergic treatment the 12 patients had experienced a median of seven episodes (range 3–28 episodes) of near syncope or syncope during a median of 10·5 months (range 1–60 months) (Table 2). During anticholinergic treatment the near syncope or syncope decreased to a median of one episode (range 0–15 episodes) during a median of 22·5 months (range 3–67 months), and six patients experienced no further symptoms. In two patients (cases 11 and 12) the frequency of symptoms was unchanged or worse. One patient (case 10) had a reduction in the number of episodes of syncope after starting on propantheline bromide; however, he continued to experience syncope and, because of his occupation, a permanent pacemaker was placed and no further episodes of syncope were reported. In general propantheline bromide was well tolerated at a dose of 15 mg. One patient (case 9) required a reduction in the dosage to 7·5 mg three times daily because of constipation; his symptoms remained well controlled during the next five years. Four patients complained of dry mouth, and one patient complained of blurred vision; however, these side effects were slight and the patients continued to take medication.

## Discussion

The patients in this study had experienced near syncope or syncope on many occasions, and the only abnormality identified after extensive neurological and cardiac investigation was evidence of an increase in vagal tone at the time of electrophysiological testing. Coincidental pronounced variations in vagal tone will complicate the proof of a proposed correlation between the results of electrophysiological testing and clinical events. None the less, anticholinergic treatment aimed at reducing the increased vagal tone was associated with a considerable reduction in the frequency of near syncope or syncope, and this finding supports a cause and effect relation. We did not subject the overall frequency of near syncope or syncope before and after anticholinergic treatment to statistical analysis because such events are sporadic and a recent episode could have prompted medical examination. Also the occurrence of clusters of episodes of syncope could have produced a spuriously high pretreatment frequency in our patients.

Our definition of increased vagal tone at the time of electrophysiological testing is arbitrary but it is consistent with that in published reports.[6 7] Although primary atrioventricular nodal disease could have been responsible for these electrophysiological findings and is also reversed by parasympathetic blockade,[9] it is unlikely that our patients had this abnormality since they did not show progressive atrioventricular conduction abnormalities. The findings during long term follow up, during which no other causes for the near syncope or syncope emerged, and the apparent response to specific anti-

Table 2 *Duration and frequency of syncopal events* before and during anticholinergic treatment*

| *Case No* | *Before* | | *During* | |
|---|---|---|---|---|
| | *Duration (mnths)* | *Episodes (No)* | *Duration (mnths)* | *Episodes (No)* |
| 1 | 4 | 13 (S, N) | 17 | 0 |
| 2 | 12 | 3 (S) | 9 | 0 |
| 3 | 18 | 8 (S, N) | 67 | 0 |
| 4 | 36 | 4 (S) | 28 | 0 |
| 5 | 3 | 6 (S) | 6 | 0 |
| 6 | 9 | 28 (S, N) | 4 | 0 |
| 7 | 1 | 3 (S) | 36 | 3 (N) |
| 8 | 48 | 15 (S, N) | 50 | 2 (S) |
| 9 | 60 | 25 (N) | 61 | 2 (N) |
| 10 | 1 | 10 (S) | 3 | 4 (S) |
| 11 | 5 | 3 (S, N) | 46 | 15 (N) |
| 12 | 12 | 4 (S) | 14 | 6 (S) |
| Median (range) | 10·5 (1–60) | 7 (3–28) | 22·5 (3–67) | 1 (0–15) |

*N, near syncope; S, syncope.

cholinergic treatment support the suggestion that increased vagal tone was the underlying factor responsible for the presenting symptoms. Mechanisms other than increased vagal tone could have been operating, however; for example, an increased sensitivity to acetylcholine or a decreased activity of acetylcholine esterase at the nerve terminal. These factors were not investigated in this study.

Excessive resting vagal tone has been reported in some cases. These are usually young people or highly trained athletes with reversible atrioventricular block on electrocardiography.[10 11] They are usually symptom free, although there are reports of a few otherwise healthy individuals with recurrent and debilitating episodes of syncope and near syncope with evidence of increased vagal tone as their only clinical abnormality.[1–4] The consequences of vasovagal episodes are usually not serious because there are warning symptoms before loss of consciousness. Our patients, however, experienced episodes of near syncope or syncope that occurred without provocation or were not associated with the typical prodrome of pallor, sweating, and nausea. In some situations such attacks could be life threatening, and they must limit activities such as driving and working in circumstances that are potentially hazardous.

The therapeutic options in patients with enhanced vagal tone are complicated by the fact that a vasovagal event has parasympathetic and sympathetic components—namely, bradycardia and a reduction in peripheral vascular resistance.[12 13] Treating the bradycardia may not necessarily improve the symptoms if there is an important additional vasodepressive component. None the less, anticholinergic treatment to prevent bradycardia was effective in 10 patients in this study and was effective in a single patient with syncope and abnormal atrioventricular refractoriness reversed by atropine described by DiMarco *et al.*[5] Propantheline bromide was well tolerated; however, the male patients in this study were young (mean age 34 years) and unlikely to have the urinary retention that occurs in older patients on this agent.

The effectiveness of a permanent pacemaker for treating vasovagal syncope has been reported by other workers in small numbers of patients,[2 5 14] and the one patient in this study who received a pacemaker has remained symptom free. Benditt *et al* reported the beneficial effect of theophylline in patients with recurrent bradycardias.[15] Thus, pacemakers should probably be reserved for patients with severe symptoms who do not respond adequately to theophylline or anticholinergic agents.

This study does not imply that patients who have a vasovagal episode should undergo electrophysiological testing. In most patients the history indicates the diagnosis, and loss of consciousness may be avoided by lying down when the warning symptoms occur. In patients who have recurrent vasovagal episodes that are not necessarily associated with a provocative event or that have a limited prodrome, the use of anticholinergic agents seems justified. As reported in this study patients occasionally present with recurrent near syncope or syncope with no identifiable cause. In such patients the results of electrophysiological testing may be normal except for evidence suggestive of increased vagal tone. Anticholinergic agents are worth trying in these patients.

The clinical implications of this study are important for patients who have near syncope or syncope with clinical or electrophysiological features compatible with increased vagal tone as their only identifiable abnormality. Whether this entity represents excessive vagal tone or another form of atrioventricular nodal dysfunction that becomes normal on atropine is not particularly important. In general, permanent pacemaker implantation can be avoided in these patients, and anticholinergic agents are worth trying.

This investigation was supported in part by a grant from the Institute of Cardiovascular Research, Brisbane, Australia.

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*Br Heart J* 1986; **55**: 58–66

# Haemostatic function in myocardial infarction

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SUMMARY Coagulation factor VIII, von Willebrand factor, antithrombin, fibrinogen, plasminogen activator capacity, and inhibitors of fibrinolysis, including a recently discovered fast inhibitor of tissue plasminogen activator, were measured three to six months after myocardial infarction in 116 male and 32 female patients aged $<45$ and in 136 age and sex matched random controls. Plasma concentrations of fibrinogen and the fast inhibitor of tissue plasminogen activator were raised in male patients (with or without correction for orosomucoid levels, blood group distribution, tobacco and alcohol consumption, and weight/height index) and plasminogen activator capacity was reduced. In female patients the concentrations of factor VIII, von Willebrand factor, the fast inhibitor of tissue plasminogen activator, $\alpha_2$-antiplasmin, and C1 inhibitor were significantly increased. The increase in factor VIII concentrations depended strongly on a persisting inflammatory response. Multivariate analysis indicated that a combination of fibrinogen and tissue plasminogen activator inhibitor concentrations gave the best independent discrimination between male patients and controls. For female patients the best combination was von Willebrand factor and tissue plasminogen activator inhibitor. Male patients with multiple vessel atheromatosis at coronary angiography had higher fibrinogen concentrations than those with atheromatosis of a single vessel. Atheromatosis was defined as sharp-edged, plaque-like, or irregular indentations, often multiple, into the vessel lumen without features suggesting fibromuscular hyperplasia.

Several mechanisms have been suggested to explain the pathogenesis of ischaemic heart disease. According to the thrombogenic theory of atherogenesis,[1] hypercoagulability may be a prerequisite not only for the development of thrombotic complications but also for the pathogenesis of atherosclerosis. Impaired fibrinolysis at the onset and during the course of myocardial infarction is viewed mainly as a reduction in defensive capacity while coronary occlusion and fibrin formation are under way.

Most studies of haemostatic function in patients with previous myocardial infarction have focused on platelet function. In general, studies including tests of blood coagulation and fibrinolysis[2–7] have been conducted in the acute phase and the patients studied have been heterogenous with regard to age, medication, and coexisting disorders. Furthermore, the presence and extent of coronary atherosclerosis has not been assessed by angiography.

Young adults with ischaemic heart disease constitute an ideal group in which to study the factors operating early in atherogenesis and arterial thromboembolism. We therefore performed a comprehensive investigation of blood coagulation and fibrinolysis in consecutive patients who had survived a definite myocardial infarction before the age of 45 and in whom coronary angiography had been performed. We measured various coagulation variables including factor VIII, von Willebrand factor, antithrombin, and fibrinogen. Fibrinolytic function was studied by determination of plasminogen activator capacity and possible inhibitors of fibrinolysis, including the recently discovered fast inhibitor of tissue plasminogen activator.

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Accepted for publication 3 September 1985

## Patients and methods

### STUDY GROUPS

Between May 1980 and September 1982, 163 patients aged $<45$ were admitted with definite myocardial infarction[8] to the eleven hospitals in Stockholm County with intensive care units. Of these, 137 were male and 26 were female. Six male patients had a history of recurrent infarctions. Fifteen patients died during the stay in hospital. The 148 consecutive survivors were subsequently referred to the Department of Medicine, Danderyd Hospital, for haemostatic, metabolic, and cardiological investigations. Two further patients died shortly after discharge from hospital. Eight patients declined the investigation and for other reasons a complete evaluation was not performed in two patients. To enlarge the female patient group, twelve more women who had myocardial infarction between October 1982 and December 1983 were also included in the study. Thus we studied 116 male patients (92% of male survivors) and 32 female patients (94% of female survivors). All patients were investigated as outpatients 3–6 months after infarction. Clinical data were abstracted from the medical records acquired on admission to the intensive care units. In addition, a medical history was obtained by a structured interview and questionnaires at the time of this study.

Most (127 cases) patients had no angina or only mild angina (New York Heart Association classes I-II) during the early post-infarction period. Severe peripheral atherosclerosis with incapacitating intermittent claudication was present in two patients and manifest diabetes in fourteen. Coronary bypass surgery was not performed in any of the patients in the period between onset of infarction and this study. One patient had been operated upon six years before the study. There were no signs of cardiac decompensation in any of the patients at the time of the haemostatic evaluation.

Two patients were initially receiving anticoagulants because of thromboembolic complications during the acute phase. They were investigated at least two months after the end of the treatment. Oral contraception had been discontinued upon admission to hospital in five women. One woman in the control group was taking oral contraceptives at the time of the study.

For each patient a control subject from the same neighbourhood was randomly selected from a general register of all residents in the county after matching for age and sex. Previous medical history and risk factors were established in the controls in the same way as they were in the patients. None of the controls had a history suggestive of angina or electrocardiographic signs indicative of ischaemic heart disease during a maximal exercise stress test (Minnesota codes 4·1 and 4·2).

### BLOOD SAMPLING

Blood samples for evaluation of the haemostatic system were drawn three to six months (mean (SD) 3·5 (1·2); range 2·5–12 months) after the onset of myocardial infarction, at which time the patients were considered to be in a stable clinical and metabolic state. Matched controls were investigated simultaneously with the patients to avoid any influence of seasonal variations on group comparisons. In both patients and controls blood sampling was evenly distributed over the year. Participants had been given written instructions to avoid platelet inhibiting treatment in the 10 days before blood sampling. All subjects were free from symptoms of infectious disease at the time of blood sampling and they had been fasting for 12 hours. Antecubital vein puncture with a 1·4 mm Wassermann needle (TSK Laboratories, Japan, Size DIM $1{\cdot}4\times45$ mm) was performed between 8.00 and 9.30 am after 10 minutes' rest in the supine position. The first 5 ml of blood was discarded, then 9 ml venous blood was taken into 1 ml trisodium citrate (0·13 mol/l) pH 7·5, and was immediately and thoroughly mixed. After centrifugation at room temperature for 20 min at 4000 *g*, plasma was dispensed into plastic tubes and kept frozen at −70°C until it was tested.

### LABORATORY METHODS

Factor VIII was determined by a two stage thrombin generation assay[9] and von Willebrand factor by quantitative electroimmunoassay.[10] Antithrombin antigen and activity were measured by radial immunodiffusion[11] and a chromogenic peptide substrate method.[12] Fibrinogen was analysed by a polymerisation test.[13] Plasminogen activator activity was determined by the fibrin plate method[14] with euglobulin precipitates. Urokinase (Loevens, Ballerup, Denmark) was used as an internal standard and the results were expressed in Plough units (PU). Plasminogen activator release was provoked by venous stasis obtained by a tourniquet applied to the upper arm at 100 mm Hg for 10 minutes. The difference in plasminogen activator activity between samples drawn before and after venous stasis was used as a measure of plasminogen activator capacity. This method primarily measures tissue plasminogen activator activity. The fast inhibitor of tissue plasminogen activator,[15] $\alpha_2$-antiplasmin,[16] prekallikrein,[17] kallikrein inhibiting activity,[17] and C1 inhibitor[18] were measured by methods that use chromogenic peptide substrates.

In addition we calculated the ratio of von

Willebrand factor to factor VIII, which has been suggested as being a useful index of hypercoagulability,[19] and the ratio of antithrombin activity to antigen. The acute phase reactant orosomucoid was determined by electroimmunoassay.[10] For technical reasons analyses of kallikrein inhibiting activity and C1 inhibitor were only performed in every second male subject.

### UNITS FOR VARIABLES

Assays of all haemostatic variables except the fast inhibitor of tissue plasminogen activator were calibrated against an internal plasma pool obtained from 20 healthy men (aged 54·6 (5·3), range 44–61 years). The results were expressed as percentages of the internal standard, which is deemed to contain 100%. Internal standards for factor VIII and von Willebrand factor were calibrated against the 1st and 8th British plama standards (66/335 and 78/506, National Institute for Biological Standards and Controls, London). Results from analysis of the fast inhibitor of tissue plasminogen activator were expressed as previously described.[15]

### CORONARY ANGIOGRAPHY

Coronary angiography was performed by the percutaneous transfemoral technique in 133 patients (107 men and 26 women) three to six months after myocardial infarction (mean (SD) 4·4 (1·5), range 1–12). Angiograms were routinely obtained both before and five minutes after the administration of sublingual glyceryl trinitrate.

The coronary angiograms were allocated to one of the following four groups: 1, normal coronary angiogram; 2, occlusion or stenosis of a single vessel—no other definite angiographic abnormalities; 3, atheromatosis in a single vessel with or without occlusion or stenosis in the same or any other vessel; 4, atheromatosis of multiple vessels with or without occlusion or stenosis of any vessel.

Atheromatosis was defined as sharp-edged, plaque-like, or irregular, indentations, often multiple, into the vessel lumen without features suggesting fibromuscular hyperplasia. One single stenosis with smooth contours or a single occlusion, in the absence of additional changes, was not classified as atheromatosis, whereas multiple lesions always were. In addition to this classification patients were divided into traditional coronary artery disease categories, according to the number of major coronary arteries with haemodynamically important lesions.[20] All angiograms were interpreted by one of us (AS) without knowledge of the clinical history or haemostatic profile of the patient.

### ADDITIONAL RISK INDICATORS

For calculation of the average tobacco consumption, one cigarette was considered to be equivalent to one gram, one cigarillo to two grams, and one cigar to five grams of tobacco. The tobacco consumption of pipe smokers was calculated by dividing by seven the weekly consumption in grams. Cumulative tobacco consumption before myocardial infarction was estimated as cigarette-years. Figures on alcohol consumption were based on a structured interview and questionnaires and expressed as grams of absolute alcohol consumed during one month. Body weight was measured with subjects dressed in ordinary indoor clothing without jacket or shoes. Blood pressure was measured in the supine position after five minutes' rest. Hyperlipoproteinaemias were defined according to the World Health Organisation classification.[21] All subjects had been evaluated by preparative lipoprotein ultracentrifugation[22] and agarose lipoprotein electrophoresis.[23] The cut-off limits for the different lipoprotein phenotypes were set to the 90th percentile of the very low density lipoprotein triglyceride and low density lipoprotein cholesterol values in age and sex matched random controls. Manifest diabetes mellitus was defined as being present when fasting hyperglycemia (whole blood) exceeded 7·0 mmol/l. Blood glucose was measured by a glucose oxidase method.[24] Oral glucose tolerance had been assessed in all patients after ingestion of 1·75 g glucose/kg body weight and the criteria for reduced glucose tolerance suggested by Efendic *et al*[25] were applied.

### STATISTICAL METHODS

The statistical methods used were those recommended by Snedecor and Cochran.[26] Proportions were compared by the $\chi^2$ test with Yates's correction. Statistical significance for differences in haemostatic variables between groups was tested by one-way analysis of variance and two-tailed $t$ tests. Significance testing of selected pairs of values after analysis of variance was performed by the Tukey studentitised range method. Coefficients of skewness and kurtosis were used to test deviations from a normal distribution, and logarithmic transformation of the individual values of skewed variables was performed before statistical analysis and testing for significance. Differences between groups were further studied by analysis of covariance which enabled us to control for concomitant group differences in other variables which may have influenced blood coagulation or fibrinolysis. Stepwise multiple discriminant analysis was performed to evaluate the independent discriminant value of the haemostatic variables. Variables reflecting smoking habits,

Table 1 *Characteristics of patients and controls (mean (SD))*

| | *Male* | | | *Female* | | |
|---|---|---|---|---|---|---|
| | *Patients (n=116)* | *Controls (n=116)* | *p value* | *Patients (n=32)* | *Controls (n=17)* | *p value* |
| Age (yr) | 39·8 (3·9) | 39·9 (3·9) | NS | 38·7 (4·6) | 39·1 (4·4) | NS |
| Blood groups (n) A/AB/B/O | 52/8/18/38 | 48/10/15/43 | NS | 16/2/5/9 | 9/0/2/6 | NS |
| Orosomucoid (g/l) | 0·46 (0·17) | 0·39 (0·10) | <0·001 | 0·53 (0·21) | 0·36 (0·09) | <0·001 |
| Smoking habits (n): | | | | | | |
| Present smoker | 46 | 45 | <0·001 | 13 | 6 | <0·001 |
| Former smoker | 63* | 30 | | 13† | 0 | |
| Non-smoker | 7 | 41 | | 6 | 11 | |
| Tobacco consumption: | | | | | | |
| Present (g/day) | 6·5 (10·1) | 8·0 (12·5) | NS | 3·6 (5·5) | 4·4 (7·4) | NS |
| Cumulative (cigarette-years) | 411 (226) | 198 (218) | <0·001 | 310 (176) | 107 (154) | <0·001 |
| Alcohol consumption (g/month) | 415 (381) | 623 (388) | <0·001 | 274 (289) | 209 (135) | NS |
| Hypertension (n) | 29 | 12 | <0·001 | 12 | 1 | <0·001 |
| Hyperlipoproteinaemia (n): | | | | | | |
| IIa | 31 | 10 | <0·001 | 2 | 3 | <0·001 |
| IIb | 8 | 2 | | 18 | 0 | |
| III | 3 | 0 | | 3 | 0 | |
| IV | 33 | 7 | | 7 | 1 | |
| Diabetes (n): | | | | | | |
| Type I | 2 | 0 | <0·001 | 7 | 0 | <0·001 |
| Type II | 4 | 0 | | 1 | 0 | |
| Decreased oral glucose tolerance (n) | 35 | 10 | | 2 | 0 | |
| Weight/height index weight/(height—100) (kg/cm) | 1·06 (0·13) | 0·99 (0·12) | <0·001 | 0·97 (0·1) | 0·91 (0·15) | NS |

*55 and †11 patients stopped smoking at the time of the infarction.
NS, not significant.

alcohol consumption, and stature, as well as ABO blood groups were entered as forced variables.

ETHICAL CONSIDERATIONS

All subjects gave their informed consent to the study. The study protocol was approved by the regional ethical committee.

## Results

CLINICAL CHARACTERISTICS AND RISK INDICATORS

Table 1 gives clinical characteristics and conventional risk indicators in patients and controls. Orosomucoid concentrations were significantly increased in both patient groups. Blood group distribution was similar in patients and controls. Smoking habits were identical in the two groups at the time of the haemostatic evaluation. There was a pronounced overrepresentation of former smokers in the patient groups, however, most of whom had stopped smoking at the time of infarction. Accordingly, cumulative lifetime tobacco consumption was much higher in patients. Alcohol consumption was higher in male controls than in male patients, whereas no differences were seen between the female study groups. More patients than controls were found to have hyperlipoproteinaemia, manifest diabetes, or reduced oral glucose tolerance. In addition, the weight/height index was higher in the young male post-infarction patients.

As shown in Table 2 a markedly higher proportion of female patients (16/26) than male patients (27/107) had no definite angiographic signs of coronary atheromatosis ($\chi^2=10·997$, $p<0·001$). Similarly the distribution of the female patients in coronary artery disease categories differed from that of the male patients, with a higher proportion of female patients having insignificant or single vessel disease ($\chi^2=6·486$, $p<0·05$).

HAEMOSTATIC VARIABLES IN PATIENTS AND CONTROLS

Table 3 gives the plasma concentrations of the haemostatic variables in patients and controls. Because sex differences were found in the plasma concentrations of some haemostatic variables male and female subjects were compared separately. Differences between patients and controls were also evaluated by analysis of covariance with orosomucoid concentration alone and with tobacco consumption, alcohol consumption, weight/height index, and ABO blood group as covariates.

The fibrinogen concentration was higher in male patients than in male controls. The difference in fibrinogen concentration between male subjects persisted when the analysis was performed with all selected covariates (mean (SD)) (3·42 (0·08) *vs* 3·16 (0·08) g/l, $p<0·05$), but was lost when orosomucoid level alone was used as a covariate. Mean fibrinogen values were higher in female patients than in controls, but the difference was not statistically significant.

Table 2 *Coronary angiographic findings in male and female patients*

| | *Classification according to presence and extension of coronary atheromatosis* | | | |
|---|---|---|---|---|
| | *Normal angiogram* | *Single occlusion/stenosis no atheromatosis* | *Single vessel atheromatosis* | *Multiple vessel atheromatosis* |
| Male patients (n=107) | 7 | 20 | 12 | 68 |
| Female patients (n=26) | 5 | 11 | 3 | 7 |
| | *Classification according to number of major coronary arteries with haemodynamically important lesions* | | | |
| | *Insignificant disease* | *Single vessel disease* | *Double vessel disease* | *Triple vessel disease* |
| Male patients (n=107) | 8 | 42 | 36 | 21 |
| Female patients (n=26) | 5 | 15 | 4 | 2 |

The concentrations of factor VIII or von Willebrand factor were similar in male patients and male controls. In contrast these factors were significantly higher in female patients than in female controls. The increase in concentration of von Willebrand factor in female patients was independent of background group differences in basic characteristics considered in covariance analysis (165·4(11·4) *vs* 95·1(16·3)%, p<0·01), whereas the difference in factor VIII level was highly correlated with increased orosomucoid concentration in the patient group. There were no significant differences between male or female patients and controls for the ratio of von Willebrand factor to factor VIII. Antithrombin concentrations as measured with the two different methods and antithrombin ratios were similar in patients and controls of both sexes.

The plasminogen activator capacity (difference in plasminogen activator activity values measured before and after venous occlusion) was decreased in both male and female patients. The difference between male patients and controls persisted after control of group differences in orosomucoid concentrations alone (0·35 (0·06) *vs* 0·57 (0·06) PU, p<0·01) or in combination with all other covariates (0·37 (0·07) *vs* 0·56 (0·06) PU, p<0·05). The significantly lower plasminogen activator capacity in female patients compared with that in female controls, however, was eliminated in the covariance analyses. The concentration of the fast inhibitor of tissue plasminogen activator was considerably increased in both patient groups and the group differences remained after correction for confounding factors.

A slight increase in antiplasmin concentration in male patients did not remain significant in the covariance analyses, whereas the moderately increased antiplasmin concentration in the female patients was not influenced by the selected covariates taken together (112·1 (4·2) *vs* 103·5 (3·1)%, p<0·05). A small but statistically highly significant increase in prekallikrein concentration in male patients was reduced and did not reach statistical significance in analysis using all covariates. In female patients a modest increase in prekallikrein concentration was entirely dependent on increased orosomucoid levels. This was also the case for kallikrein inhibiting activity, whereas the increase in C1 inhibitor concentration in female patients was only marginally influenced by the selected covariates (126·9 (5·0) *vs* 100·9 (6·6)%, p<0·05). Concentrations of kallikrein inhibiting activity and C1 inhibitor were almost identical in male patients and controls.

Analysis of individual data on male patients showed that 17% had values of factor VIII above the 90th percentile of matched controls, 22% had

Table 3 *Haemostatic variables in patients and random controls (mean (SD))*

| *Measurement* | *Male* | | | *Female* | | |
|---|---|---|---|---|---|---|
| | *Patients (n=116)* | *Controls (n=116)* | *p value* | *Patients (n=32)* | *Controls (n=17)* | *p value* |
| Fibrinogen (g/l) | 3·52 (1·07) | 3·08 (0·81) | <0·01 | 4·03 (1·31) | 3·40 (1·01) | NS |
| Factor VIII (%) | 105·0 (32·0) | 99·7 (35·7) | NS | 160·1 (78·8) | 91·8 (38·0) | <0·001 |
| vWFAg (%) | 113·6 (54·5) | 103·7 (40·9) | NS | 162·2 (68·8) | 100·1 (35·1) | <0·01 |
| ATS (%) | 104·9 (10·2) | 105·1 (9·2) | NS | 105·9 (13·3) | 101·7 (8·8) | NS |
| ATAg (%) | 103·0 (12·0) | 103·4 (9·9) | NS | 105·4 (11·7) | 98·7 (11·7) | NS |
| PA capacity (PU) | 0·31 (0·46) | 0·58 (0·73) | <0·01 | 0·28 (0·31) | 0·43 (0·32) | <0·05 |
| t-PA inhibitor (AU/ml) | 4·36 (3·18) | 2·78 (1·93) | <0·001 | 3·80 (1·59) | 2·06 (0·69) | <0·01 |
| Antiplasmin (%) | 103·1 (10·8) | 99·9 (11·4) | <0·05 | 112·9 (15·5) | 101·7 (6·7) | <0·05 |
| Prekallikrein (%) | 104·4 (14·7) | 97·7 (15·7) | <0·001 | 105·1 (28·9) | 93·3 (13·4) | NS |
| Kallikrein inhibiting activity (%) | 111·1 (15·2) | 111·3 (12·7) | NS | 117·2 (22·7) | 97·2 (9·5) | <0·05 |
| C1 inhibitor (%) | 114·7 (17·9) | 114·0 (16·3) | NS | 126·9 (14·3) | 101·4 (11·0) | <0·001 |
| Ratio vWFAg:FVIII | 1·09 (0·42) | 1·03 (0·39) | NS | 1·10 (0·49) | 1·15 (0·35) | NS |
| Ratio ATS.ATAg | 1·02 (0·09) | 1·02 (0·09) | NS | 1·06 (0·08) | 1·04 (0·08) | NS |

vWFAg, von Willebrand factor; ATS, antithrombin activity, ATAg, antithrombin antigen; PA, plasminogen activator; t-PA inhibitor, fast inhibitor of tissue plasminogen activator; FVIII, factor VIII; PU, plough units, AU, arbitrary units.

Table 4 *Haemostatic variables in male patients grouped according to the presence and extent of coronary atheromatosis*

| *Measurement* | *Normal angiogram (n=7)* | *Single occlusion or stenosis (n=20)* | *Single vessel atheromatosis (n=12)* | *Multiple vessel atheromatosis (n=68)* | *F value* | *p value* |
|---|---|---|---|---|---|---|
| Fibrinogen (g/l) | 3·16 (1·23) | 3·17 (0·55) | 2·98 (0·52) | 3·76 (1·18) | 3·65 | 0·015 |
| Factor VIII (%) | 117·4 (36·2) | 93·4 (31·0) | 102·3 (31·6) | 104·6 (28·0) | 1·25 | 0·295 |
| vWFAg (%) | 100·0 (49·6) | 96·1 (31·6) | 117·4 (49·1) | 116·4 (58·7) | 0·84 | 0·478 |
| ATS (%) | 107·9 (11·0) | 105·9 (9·5) | 104·1 (9·2) | 105·3 (10·6) | 0·21 | 0·886 |
| ATAg (%) | 102·4 (14·0) | 105·3 (12·7) | 100·3 (6·8) | 103·5 (12·4) | 0·42 | 0·738 |
| PA capacity (PU) | 0·15 (0·13) | 0·35 (0·47) | 0·32 (0·51) | 0·31 (0·45) | 0·65 | 0·585 |
| t-PA inhibitor (AU/ml) | 6·86 (9·52) | 3·82 (1·81) | 2·90 (1·82) | 4·78 (3·03) | 0·48 | 0·694 |
| Antiplasmin (%) | 98·6 (10·2) | 99·8 (11·1) | 102·3 (8·0) | 104·4 (11·1) | 1·24 | 0·298 |

vWFAg, von Willebrand factor; ATS, antithrombin activity, ATAg, antithrombin antigen, PA, plasminogen activator, t-PA inhibitor, fast inhibitor of tissue plasminogen activator.

values of von Willebrand factor above the 90th percentile, and 37·5% had values of the fast inhibitor of tissue plasminogen activator about the 90th percentile (values above 135% for factor VIII, 150% for von Willebrand factor, and 3·5 AU/ml for the fast inhibitor of tissue plasminogen activator). Similar analysis of plasminogen activator capacity data showed that 20·8% of male patients had values below the 10th percentile of control subjects (values below 0·15). Limited numbers in the control group prevented this analysis in female patients.

In stepwise multiple discriminant analysis, concentrations of fibrinogen and the fast inhibitor of tissue plasminogen activator emerged as the haemostatic variables that gave the best independent discrimination between male patients and controls. The independent discriminatory power of the fast inhibitor of tissue plasminogen activator was entirely lost, however, when tobacco consumption, regular alcohol intake, and weight/height index were introduced in the discriminant function. In women concentrations of von Willebrand factor and the fast inhibitor of tissue plasminogen activator gave the best independent discrimination between patients and controls, irrespective of the introduction of possible confounding variables. When we used the two sets of haemostatic variables contained in the discriminant functions we correctly classified 65% of male and female patients, with slightly higher values for controls.

### CORRELATIONS BETWEEN HAEMOSTATIC VARIABLES AND CORONARY ANGIOGRAPHIC FINDINGS IN MALE PATIENTS

Tables 4 and 5 show the concentration of some haemostatic variables in male patients grouped according to presence and extension of coronary atheromatosis or number of significantly diseased major coronary arteries.

Analysis of variance indicated differences in fibrinogen concentration among patients grouped according to presence and extension of coronary atheromatosis (Table 4). Mean fibrinogen concentration in male patients with multiple vessel atheromatosis at angiography was significantly higher than that in male patients with single vessel atheromatosis ($p < 0.05$, as tested by the Tukey procedure). The mean fibrinogen concentration in patients with an entirely normal coronary angiogram and with single vessel occlusion/stenosis and no other angiographic evidence of atheromatosis resembled that in patients with coronary atheromatosis demonstrable in only one of the major coronary arteries.

When male patients were grouped according to the number of vessels with haemodynamically im-

Table 5 *Haemostatic variables in male patients grouped according to the number of major coronary arteries with haemodynamically important lesions (mean (SD))*

| *Measurement* | *Insignificant disease (n=8)* | *Single vessel disease (n=42)* | *Double vessel disease (n=36)* | *Triple vessel disease (n=21)* | *F value* | *p value* |
|---|---|---|---|---|---|---|
| Fibrinogen (g/l) | 3·24 (1·16) | 3·41 (1·03) | 3·62 (1·05) | 3·68 (1·20) | 0·39 | 0·761 |
| Factor VIII (%) | 118·1 (33·6) | 96·9 (27·7) | 106·2 (30·7) | 104·0 (28·8) | 1·38 | 0·254 |
| vWFAg (%) | 107·1 (50·2) | 108·1 (65·0) | 123·4 (44·9) | 100·6 (42·5) | 0·94 | 0·422 |
| ATS (%) | 107·9 (10·2) | 106·4 (9·3) | 106·9 (9·3) | 100·4 (12·0) | 2·22 | 0·091 |
| ATAg (%) | 104·8 (14·6) | 104·2 (11·4) | 103·2 (11·5) | 101·7 (13·3) | 0·22 | 0·632 |
| PA capacity (PU) | 0·13 (0·12) | 0·36 (0·48) | 0·27 (0·34) | 0·34 (0·62) | 0·79 | 0·505 |
| t-PA inhibitor (AU/ml) | 5·34 (8·19) | 4·04 (2·27) | 4·43 (3·29) | 4·43 (1·35) | 0·40 | 0·751 |
| Antiplasmin (%) | 99·4 (9·7) | 103·2 (11·9) | 103·7 (9·9) | 102·4 (12·4) | 0·34 | 0·795 |

vWFAg, von Willebrand factor, ATS, antithrombin activity, ATAg, antithrombin antigen; PA, plasminogen activator, t-PA inhibitor, fast inhibitor of tissue plasminogen activator portant lesions (Table 5), there was a tendency for patients with triple vessel disease to have lower antithrombin activity values than the remainder of the patients. This difference was not significant as analysed by the Tukey studentitised range method.

No significant differences in factor VIII and the von Willebrand factor were noted between patients grouped according to two angiographic classification systems, nor were there significant group differences for any of the fibrinolytic variables.

No significant differences were found in the few female patients grouped according to angiographic findings.

## Discussion

So far most of the epidemiological and aetiological research on ischaemic heart disease has mainly dealt with conventional risk factors such as smoking, hypertension, and different hyperlipoproteinaemias—studies on the haemostatic system have been scarce. Young adults with myocardial infarction probably represent a heterogenous group.[27-29] In most cases rapidly progressing coronary atherosclerosis is the underlying disease. In a minority, however, other predisposing factors may be operating. Since haemostatic function has been implicated in atherogenesis as well as in thromboembolic disorders, we decided to investigate the function of blood coagulation and fibrinolysis in patients with premature ischaemic heart disease. No such studies have yet been reported in representative and sufficiently large groups of young post-infarction patients.

Stepwise discriminant analysis indicated that concentrations of fibrinogen and the fast inhibitor of tissue plasminogen activator in men and von Willebrand factor and the fast inhibitor of tissue plasminogen activator in women were significant discriminants of myocardial infarction. There was a striking sex difference in the distribution of patients between the angiographic subgroups: Sixty two percent (16/26) of the female patients who had coronary angiography had no definite signs of atheromatosis nor did 25% (27/107) of male patients. Male patients with a coronary angiogram showing severe atheroma tended to have higher plasma fibrinogen concentration than patients without angiographic evidence of coronary atheromatosis. There was also a tendency for antithrombin activity values to be low in male patients with triple vessel disease.

These data suggest that disturbances of blood coagulation and fibrinolysis might have considerable independent significance for the development of myocardial infarction in young women because they predispose them to coronary thrombosis. The haemostatic alterations seen in male patients might primarily be involved in the evolution of coronary atherosclerosis. These disturbances, however, might also play a part in the precipitation of infarction in individuals with severe widespread coronary atheroma.

The interpretation of the present data on fibrinogen is not clear. In previous studies[30-32] increased fibrinogen concentrations have been found in patients with ischaemic heart disease. Furthermore fluid dynamic factors have been implicated in the siting of atherosclerotic lesions.[33] An association between blood viscosity and extension of coronary artery disease, partly due to increased fibrinogen concentrations, has been demonstrated in one angiographic study.[34]

Our findings in male patiens do not confirm earlier observations of higher plasma concentrations of von Willebrand factor in patients with angiographic evidence of atherosclerosis.[35] Furthermore, data from an extensive population study[36] have suggested that factor VIII might be a predictor of subsequent cardiovascular mortality in middle aged men, whereas the concentration of von Willebrand factor was not raised in fatal cases. An increase in both the von Willebrand factor and factor VIII might indicate a hypercoagulable state. In addition there is evidence that von Willebrand factor has an atherogenic action. Raised concentrations of von Willebrand factor might thus be a primary abnormality rather than a secondary response to the intimal injury of arterial lesions.[37] In von Willebrand's disease platelets adhere to subendocardial structures,[38] and adhering platelets are believed to release a growth factor capable of inducing extensive proliferation of smooth muscle cells.[39]

A hereditary deficiency of antithrombin is a rare cause of venous thrombosis, whereas both increased and decreased concentrations of antithrombin antigen have been reported in ischaemic heart disease.[40] Low concentrations have been reported in the acute as well as in the recovery phase after myocardial infarction and in patients with angina pectoris associated with coronary atherosclerosis.[36 41] In the present study normal concentrations of antithrombin were found in both male and female patients by antigen and substrate methods. Only a few patients had low concentrations of antithrombin. The lowest antithrombin concentrations (chromogenic peptide substrate method) and ratios were seen in patients with triple vessel disease.

It has been suggested that low antithrombin concentrations in individuals with angina pectoris might reflect a slow ongoing intravascular coagulation with increased consumption of antithrombin.[40] An alternative explanation would be that of increased consumption of antithrombin due to insufficient natural protection of the atherosclerotic coronary arterial intima against blood clotting. Lower pre-existing concentrations contributing to a prethrombotic state cannot be ruled out. High concentrations of antithrombin, on the other hand, most likely represent a protective response, which may later be followed by low levels.[5]

The vessel wall content of tissue plasminogen activator, the release of tissue plasminogen activator from the endothelium, and the physiological inhibitors of fibrinolysis are regarded as the main factors regulating plasminogen activator capacity. Data from the present study suggest that the recently described rapid inhibitor of tissue plasminogen activator is an important factor in the modulation of the fibrinolytic response. The low plasminogen activator capacity found in young patients after infarction might thus primarily be due to high concentrations of this inhibitor. The additional contribution of impared tissue plasminogen activator release to the decreased plasminogen activator capacity, however, was not clarified by the present study, since tissue plasminogen activator antigen was not determined. High plasma concentrations of the fast inhibitor to tissue plasminogen activator were also found in patients investigated before coronary artery bypass operation.[42]

In female patients $\alpha_2$-antiplasmin and C1 inhibitor concentrations were also consistently raised. The clinical implication of these modest increases is, however, not obvious. The findings of increased concentrations of $\alpha_2$-antiplasmin and prekallikrein in male patients were only expressions of a non-specific inflammatory response, as was increased kallikrein inhibiting activity in female patients.

Apart from predisposing patients to thrombosis, decreased fibrinolytic capacity could theoretically promote the development of premature atherosclerosis. The similarity in the profile of changes in variables reflecting fibrinolysis in male patients with and those without definite coronary atheromatosis, as well as the considerably raised concentrations of the fast inhibitor of tissue plasminogen activator and the resultant low plasminogen activator activity in some patients with a normal coronary angiogram, however, are more indicative of a primary influence on the thrombotic element in myocardial infarction.

Do the haemostatic disturbances we report reflect a non-specific acute phase response to tissue damage and acute stress or do they represent pathogenetic mechanisms involved in the development of coronary occlusion? Unexpectedly increased concentrations of several well established acute phase reactants were found in patients as compared with random controls. Multivariate analysis that controlled for the influence of a non-specific inflammatory response showed that some haemostatic abnormalities were independent discriminants between patients and controls. Furthermore in most instances the haemostatic variables showed no or only weak correlations with the acute phase reactants. Thus, the results seem to remain valid even after a persisting non-specific acute phase response has been taken into account.

The associations of some haemostatic factors with myocardial infarction and coronary atheromatosis in this cross sectional study do not necessarily imply causation. This has to be tested in prospective studies. The findings indicate, however, that risk factors other than the conventional ones might be of importance for the evolution of ischaemic heart disease.

This study was supported by grants from the Swedish National Association against Heart and Chest Diseases, Karolinska Institutet and the Swedish Medical Research Council.

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# Post-infarction exercise testing in patients under 55 years

## *Relation between ischaemic abnormalities and the extent of coronary artery disease*

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SUMMARY Previous studies have suggested that the early post-infarction exercise test is useful in predicting the extent of coronary artery disease. The results of a heart rate limited exercise test three weeks after infarction and a symptom limited exercise test six weeks after infarction obtained by both standard 12 lead electrocardiograms and 16 lead precordial maps were compared in 100 consecutive survivors of acute myocardial infarction under 55 years of age. Exercise tests were defined as being positive on the basis of angina, ST segment depression $\geqslant 1$ mm in any electrocardiogram lead, or exertional hypotension. Multivessel disease, that is two or three vessel disease, was present in 60 patients, and three vessel disease in 22 patients. The sensitivity, specificity, and predictive value for multivessel disease of the three week test were 38%, 83%, and 76% respectively; and results for the six week test were 55%, 75%, and 77% respectively. Only 32% of patients with three vessel disease were identified at the three week test, and 59% at the six week test. Significantly more patients with multivessel and three vessel disease were identified by the symptom limited six week test. Precordial mapping offered no advantages over the standard 12 lead electrocardiogram in either the identification of patients with multivessel disease or the prediction of the distribution of coronary artery disease. Angina pectoris during the exercise test at six weeks was the single most useful predictor of multivessel disease. Multivessel disease was found in 27 (87%) of the 31 patients with angina with or without ST depression during the test at six weeks compared with 33 (48%) of the 69 patients who did not have angina during the test at six weeks.

Exercise testing in the early post-infarction period in patients under 55 years of age is of limited value in predicting the extent of coronary artery disease. It is, therefore, unreasonable to use such exercise tests to select patients for coronary arteriography after myocardial infarction. None the less angina pectoris occurring during a symptom limited exercise test six weeks after infarction is a strong predictor of multivessel disease, and coronary arteriography is recommended in these patients.

The major determinants of long term outcome after acute myocardial infarction are age,[1–3] left ventricular function,[3 4] and, in patients without severe left ventricular impairment, the extent of underlying coronary artery disease.[3 4 5] An important aspect of the management of survivors of myocardial infarction is the identification of those patients at increased risk of subsequent cardiac events. A non-invasive means of predicting the extent of coronary artery disease would therefore be useful.

Treadmill exercise testing is safe in the early post-infarction period[6] and several studies have examined its value in the prediction of the extent of coronary artery disease.[7–9] In many of the studies submaximal exercise tests were performed within three

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Accepted for publication 30 September 1985

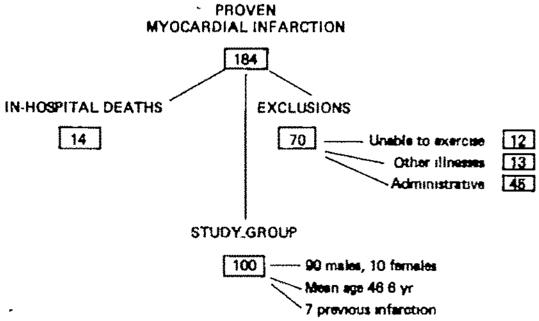

Fig. 1 *Study population.*

weeks of myocardial infarction, and significant numbers of patients with two and three vessel disease had negative tests.[9-11] Because Starling *et al* have shown that some patients develop ST depression at six weeks but not at three weeks after infarction,[12] a later maximal exercise test may detect some of these patients.

On the basis of results from previous studies the early post-infarction exercise test is being recommended as a filter for the selection of patients for coronary arteriography[13 14] and their subsequent referral for early coronary artery surgery.[7 15] Many of the studies upon which such recommendations are based have, however, included patients up to 65 or 70 years of age.[8 9 16] It may not be appropriate to apply such data to the management of younger patients in whom prophylactic interventions such as coronary artery surgery are more likely to be considered.

The main purpose of the present study was to evaluate the relation between exercise induced myocardial ischaemia early after myocardial infarction and the extent of coronary artery disease in a group of younger patients. The study was prospective and of a consecutive group of patients under 55 years who were admitted to the coronary care unit and survived acute myocardial infarction. The study design allowed us to assess the importance of the timing and intensity of exercise by comparing an early submaximal exercise test with a later maximal exercise test. We also examined the value of precordial electrocardiographic mapping during exercise since Fox *et al* have demonstrated its ability to identify the presence of left main stem or proximal left anterior descending artery lesions.[17]

## Patients and methods

### STUDY POPULATION

The study population was drawn from a consecutive group of 184 patients with proven myocardial infarction under 55 years of age and admitted to our coronary care unit between October 1981 and February 1984 (Fig. 1). Acute myocardial infarction was diagnosed when a patient presented with a history of typical chest pain lasting at least 30 minutes with characteristic electrocardiographic changes, that is a sequential rise of ST segment, inversion of T waves, and appearance of new Q waves, or a rise in either creatine phosphokinase, lactic dehydrogenase, or aspartate aminotransferase to at least twice the upper limit of the normal range. Fourteen (7·6%) of the 184 patients died in hospital after the acute event and 70 (41%) of the survivors were excluded from the study for the reasons indicated in Fig. 1. Twelve patients were unable to exercise, nine for orthopaedic or neurological reasons and three because of left ventricular failure. Thirteen patients had other serious, non-cardiac diseases which prevented them participating in the study. Of the 45 patients excluded for administrative reasons, 22 patients refused to participate in the study, six lived away from the area and had been on holiday when they had their acute infarction, and 17 patients were missed during the course of the study. The study group therefore consisted of 100 patients.

### EXERCISE TEST

All patients had a submaximal treadmill exercise test three weeks after infarction (mean 19·7 days, range 17–24 days) and a maximal treadmill exercise test six weeks after infarction (mean 42·7 days, range 35–50 days). A modified Bruce protocol was used for both tests. The submaximal three week test were terminated if (*a*) the patient developed limiting symptoms of chest pain, dyspnoea, or fatigue; (*b*) there was a sustained fall in systolic blood pressure of $>20$ mm Hg from values attained earlier during exercise; (*c*) ventricular extrasystoles occurred in runs of three or more; (*d*) there was ST segment depression of $>4$ mm, or (*e*) a heart rate of 130 beats/minute was achieved in the absence of other end points. The end points for the maximal six week test were the same except that the heart rate limitation was not applied. There were no complications.

All patients had both standard 12 lead electrocardiograms and 16 lead precordial maps[18] recorded at rest, at peak exercise, and at 1, 3, and 5 minutes after exercise.

### CORONARY ARTERIOGRAPHY

Coronary arteriography and left ventricular angiography were performed by the Judkins or Sones techniques in all patients a mean of three months after their acute myocardial infarction. The coronary arteries were viewed in multiple projections and left ventricular angiograms were recorded in both 30° right anterior oblique and either 60° left

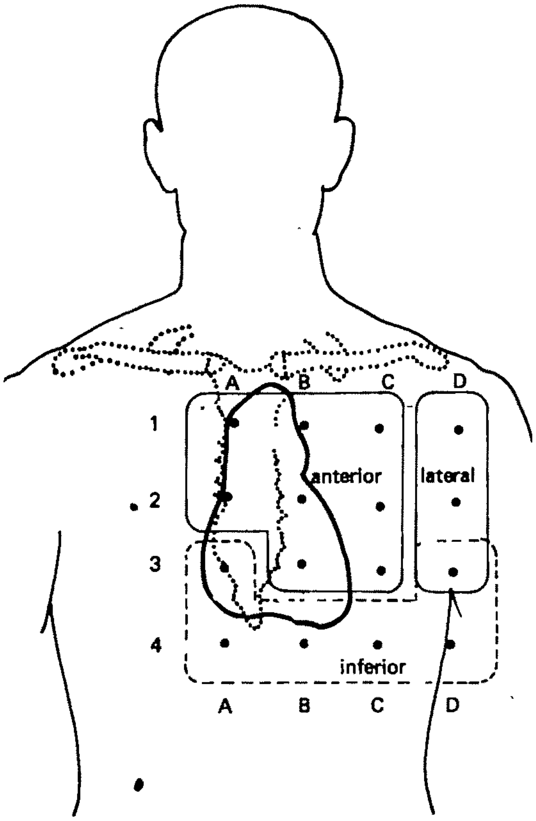

Fig 2 *Position of precordial map chest electrodes (from Fox et al[17]). For analysis of distribution of coronary artery disease the precordial map was divided into anterior, inferior, and lateral regions.*

anterior oblique or lateral projections. There were no complications. All arteriograms were reported independently by two observers (IP and RJCH) without knowledge of the exercise test data.

### DEFINITIONS

An exercise test was considered to be positive if (*a*) the patient developed angina pectoris; (*b*) there was horizontal or downsloping ST segment depression of $\geqslant 1$ mm lasting 0·08 s after the J point of the QRS complex in any of the standard leads or leads of the precordial map; or (*c*) there was an inadequate blood pressure response to exercise shown by an increase of $<10$ mm Hg in systolic blood pressure over the resting value or a sustained fall in systolic blood pressure of $>20$ mm Hg from values attained earlier during exercise.

At coronary arteriography an important stenosis was defined as one in which there was a $\geqslant 50\%$ reduction in luminal diameter of a major coronary artery in two orthogonal views. In other studies a reduction of $\geqslant 70\%$ in luminal diameter was regarded as being important (see Table 3). Stenoses in major diagonal or obtuse marginal (lateral circumflex) branches were considered to constitute left anterior descending or left circumflex artery disease respectively. The term multivessel coronary artery disease refers to important disease in two or more major coronary arteries.

For analysis and comparison of our results with those of Fox *et al*[17] we subdivided the 16 lead precordial map into anterior, inferior, and lateral regions (Fig. 2). Their study demonstrated the associations (*a*) between ST segment depression in the first row of the precordial grid and the presence of important left main stem or proximal left anterior descending artery stenoses, (*b*) between ST depression in the anterior or inferior regions and the presence of important left anterior descending or right coronary artery stenoses respectively, and (*c*) between ST depression in all three regions and the presence of important three vessel disease.

### STATISTICAL ANALYSIS

We used the $\chi^2$ test for group comparisons. McNemar's test[19] was used to evaluate the difference in exercise test results between three week and six week tests. The sensitivity, specificity, and predictive values of a positive and negative test to detect the presence or absence of multivessel disease were determined. Sensitivity was defined as the percentage of patients with multivessel coronary artery disease who had a positive test. Specificity was defined as the percentage of patients without multivessel coronary artery disease who had a negative test. The positive predictive value was defined as the percentage of patients with a positive test who had multivessel coronary artery disease. The negative predictive value was defined as the percentage of patients with a negative test who did not have multivessel coronary artery disease, that is those who had insignificant or single vessel disease.

## Results

### CLINICAL CHARACTERISTICS

The mean age of the 100 patients in the study group was 46·6 years (range 32–54 years). There were 90 men and 10 women. Seven patients had had a previous myocardial infarction. The index infarction was anterior in 45 patients and inferior in 55 patients. Only three patients were taking beta blockers at the time of their three week exercise test and four patients at the time of their six week exercise test. No patient was taking digoxin.

Table 1 *Exercise test responses at the three week and six week exercise tests derived from both standard 12 lead electrocardiograms and 16 lead precordial maps*

| | *3 weeks* | *6 weeks* |
|---|---|---|
| Positive test: | 34 | 45 |
| Angina alone | 12 | 19 |
| ST depression alone | 16 | 11 |
| Angina and ST depression | 6 | 12 |
| Inadequate blood pressure and ST depression | 0 | 3 |
| Negative test | 66 | 55 |

### ANGIOGRAPHY

Five patients were found to have no important coronary artery disease, 35 patients had important single vessel disease, 38 patients had two vessel disease, and 22 patients had three vessel disease. Multivessel coronary artery disease was present in 60 patients. Only two patients had an important left main stem lesion; in one of these the left main stem was occluded. Twenty five patients had important disease of the proximal left anterior descending artery (that is proximal to the origin of the first septal artery). Of the 55 patients with inferior infarction, 34 (62%) had multivessel disease while 26 (58%) of the 45 patients with anterior infarction had multivessel disease. This difference was not statistically significant. At the time of their exercise test six weeks after infarction 38 patients gave a clinical history of angina on exertion. Multivessel disease was detected in 28 (74%) of these patients compared with 32 (52%) of the 62 patients without clinical angina ($p < 0{\cdot}05$).

### EXERCISE TEST

Table 1 lists the exercise test responses in all patients derived from data from both the standard 12 electrocardiogram leads and the 16 lead precordial map. Only 25 (66%) of the 38 patients with a clinical history of angina six weeks after infarction developed angina during their exercise test at six weeks. An additional six patients without clinical angina experienced angina during the exercise test at six weeks (Table 1). Angina during the exercise test at six weeks proved to be a useful predictor of multivessel coronary artery disease. Multivessel disease was found in 27 (87%) of the 31 patients who had angina alone or angina with ST depression at the six week exercise test compared with 33 (48%) of the 69 patients without angina at the six week exercise test. This difference is highly significant ($p < 0{\cdot}0005$). Of the 19 patients with angina alone, 16 (84%) had multivessel disease and 8 (42%) of them had three vessel disease; and of the 12 patients with both angina and ST depression, 11 (92%) had multivessel disease, two (17%) having three vessel disease. Only four (36%) of the patients with ST depression alone had multivessel disease; and of the patients with an inadequate blood pressure response and ST depression there was one each with single, two, and three vessel disease.

Table 2 correlates the extent of coronary artery disease with the numbers of positive exercise tests at three weeks and six weeks after infarction. The results are presented separately for the 12 lead and 16 lead systems.

### 12 LEAD VERSUS 16 LEAD

At neither the three week nor the six week exercise test was 16 lead precordial mapping significantly better than the standard 12 leads in identifying those patients with multivessel disease. No patient with three vessel disease was identified by electrocardiographic mapping and not by the standard leads. Similarly no patient with a positive test on the standard 12 leads had a negative test on the precordial map. The specificity of the 16 lead system was slightly less at both three and six weeks because additional patients with single vessel disease had ST depression on the precordial map but not the standard 12 lead electrocardiogram on both occasions.

The precordial map was subdivided into anterior, inferior, and lateral regions (Fig. 2) to examine the relation between exercise induced ST depression in leads distant from those affected during the acute infarction and the extent of coronary artery disease. For comparison the standard 12 leads were also grouped as anterior (V1–V5), inferior (II, III, and aVF) and lateral (I, aVL, and V6). From data obtained at the six week exercise test important disease in the appropriate arteries (subtending electro-

Table 2 *Correlation between extent of coronary artery disease and the numbers of positive exercise tests analysed separately for standard 12 lead electrocardiogram and 16 lead precordial map*

| | *3 week test* | | *6 week test* | |
|---|---|---|---|---|
| | *12 leads* | *16 leads* | *12 leads* | *16 leads* |
| 0/SVD (n=40) | 7 | 10 | 10 | 12 |
| 2 VD (n=38) | 16 | 17 | 20 | 20 |
| 3 VD (n=22) | 7 | 7 | 13 | 13 |
| Total | 30 | 34 | 43 | 45 |

0/SVD, no disease or single vessel disease; 2 VD, two vessel disease; 3 VD, three vessel disease.

ⓐ Two vessel disease

| | | 3 week test + | 3 week test − | |
|---|---|---|---|---|
| 6 week test | + | 12 | 8 | 20 |
| | − | 4 | 14 | 18 |
| | | 16 | 22 | 38 |

(p = NS)

ⓑ Three vessel disease

| | | 3 week test + | 3 week test − | |
|---|---|---|---|---|
| 6 week test | + | 7 | 6 | 13 |
| | − | 0 | 9 | 9 |
| | | 7 | 15 | 22 |

(p<0·05)

ⓒ Multivessel disease

| | | 3 week test + | 3 week test − | |
|---|---|---|---|---|
| 6 week test | + | 19 | 14 | 33 |
| | − | 4 | 23 | 27 |
| | | 23 | 37 | 60 |

(p<0 05)

Fig. 3 *Comparison of the results of the three week and six week exercise tests in patients with two vessel disease (a), three vessel disease (b), and multivessel disease (c) using standard 12 lead data only. +, positive exercise test; —, negative exercise test.*

cardiographic regions not affected by the acute infarction) was correctly predicted by precordial mapping in 17 (65%) of the 26 patients with ST depression and by standard electrocardiogram leads in 15 (58%). The difference between the two lead systems is not significant. The remaining nine patients (of the 26) with ST depression had either insignificant (two patients) or single vessel (seven patients) coronary artery disease. There were 25 patients with important proximal left anterior descending disease. In 10 patients the vessel was occluded and in 15 patients the vessel was significantly narrowed. In nine (60%) of the 15 patients with narrowed vessels the index infarction was inferior and the precordial electrocardiogram leads had no Q waves or resting ST segment abnormalities. Only one (11%) of these nine patients developed ST depression in the first row of the precordial grid. Only one of the two patients with important left main stem disease presented with inferior infarction and he developed neither angina nor ST depression at either of the two exercise tests. The 16 lead precordial map was not therefore useful in predicting the presence of left main stem or proximal left anterior descending artery disease.

Because the 16 lead precordial map did not identify more patients with multivessel disease than the 12 standard leads, we based the comparison between the 3 week and 6 week exercise tests on data obtained with the standard 12 leads only.

### THREE WEEKS VERSUS SIX WEEKS

The sensitivity, specificity, and predictive value of a positive submaximal exercise test 3 weeks after infarction for patients with multivessel disease are 38%, 83%, and 76% respectively. The predictive value for three vessel disease is only 24%, with 15 (68%) of patients with three vessel disease having a negative exercise test. The negative predictive value of the three week test is 46%.

The sensitivity, specificity, and predictive value of a positive maximal exercise test six weeks after infarction for patients with multivessel disease are 55%, 75%, and 77% respectively. The predictive value for three vessel disease is only 30%, with nine (41%) of patients with three vessel disease having a negative exercise test. The negative predictive value of the six week test is 53%.

Only 23 (38%) of the patients with multivessel disease were identified at the three week test compared with 33 (55%) at the six week test ($p<0·05$) (Fig. 3c). Significantly more patients with three vessel disease were identified at the maximal six week test ($p<0·05$) (Fig. 3b). The difference was not significant for patients with two vessel disease (Fig. 3a).

## Discussion

The extent of underlying coronary artery disease is one of the important determinants of long term prognosis in survivors of an acute myocardial infarction.[3-5] Knowledge of its extent in individual patients would thus help greatly in the planning of long term management.

Although coronary arteriography is safe and carries very little risk,[20] its widespread use in all survivors of acute myocardial infarction is impractical. Alternative, cheaper non-invasive means of predicting the extent of coronary artery disease have therefore been sought. These could be more widely applied and used as a filter to select those patients who should proceed to coronary arteriography. Treadmill exercise testing is now widely used in this context[10] and forms a routine part of post-infarct management in many centres.

Studies examining the ability of the early post-infarction exercise test to predict the extent of coronary artery disease have produced conflicting results[7 10] (Table 3). The sensitivity of exercise testing for identifying multivessel disease varies from 56% to 96%, the specificity from 53% to 94%, and the predictive value of a positive test from 74% to 98%. Several factors might explain the differing results. Different populations have been investigated, the timing of the exercise tests has differed, different exercise protocols have been used, and the end points have differed, some being heart rate limited[9-11] and others symptom limited.[7 8] The definition of an important coronary artery stenosis has also differed. The values of an early submaximal and a later maximal exercise test in predicting the extent of coronary artery disease in the same group

Table 3 *Data from previously published studies compared with those from the present study*

| *Author* | *Patient's age (yr) (n)* | *Previous MI* | *Timing* | *Exercise test* | |
|---|---|---|---|---|---|
| | | | | *Protocol* | *End point* |
| Akhras *et al*[7] 1982 | <55 (61) | — | 2–3 wk | Bruce | Maximal |
| Starling *et al*[8] 1981 | 32–68 (57) | 19% | 2 wk | Naughton | Maximal |
| Fuller *et al*[9] 1981 | 40–64 (40) | 25% | 13 days | Modified Bruce | Submaximal |
| Schwartz *et al*[10] 1981 | 35–68 (48) | 25% | 18–22 days | Modified Bruce | Submaximal |
| Sullivan *et al*[11] 1985 | 29–64 (62) | 15% | 7–23 days | Modified Naughton | Submaximal |
| Present study | <55 (100) | 7% | 3 wk | Modified Bruce | Submaximal |
| | | 7% | 3 wk | Modified Bruce | Submaximal |
| | | 7% | 6 wk | Modified Bruce | Maximal |
| | | 7% | 6 wk | Modified Bruce | Maximal |

MI, myocardial infarction; 3 VD, three vessel disease

of patients have not been compared before.

We chose to investigate patients under 55 years because many centres still perform routine coronary arteriography on younger patients after myocardial infarction and also because prophylactic interventions are more likely to be considered in this age group.

### 12 LEAD VERSUS 16 LEAD

In their original study using precordial mapping in a small group of patients Fox *et al* suggested that 16 lead precordial mapping may show areas of ischaemia inaccessible to the standard 12 leads.[18] After infarction precordial mapping might aid identification of some of the appreciable number of patients with multivessel coronary artery disease and a negative exercise test on the conventional electrocardiogram leads.[9–11] The present study, however, has shown that the 16 lead system offers no advantages over the standard 12 leads in identifying these patients. We were also unable to confirm the findings of Fox *et al* of a correlation between ST segment changes within specific regions of the precordial grid and the distribution of coronary artery disease.[17] Although Fox *et al* were able to identify all patients, in a group suffering from stable angina, with significant left main stem or proximal left anterior descending disease, most of our patients with such lesions did not have ST depression on exercise.

The major reason for the differing results undoubtedly relates to the study populations investigated. Our patients had recently sustained an acute myocardial infarction and many (usually those with anterior infarcts) had electrocardiographic abnormalities at rest and developed ST segment elevation on exercise. Parts of the precordial grid were therefore excluded from developing ST segment depression during exercise. In addition the development of ST elevation on exercise may have prevented the development of ST depression in the reciprocal territory by generating an opposing force to the ischaemic vector.[21]

Since the 16 lead precordial map offers no advantages over the standard 12 leads the subsequent discussion is based on results using the standard 12 leads only.

### THREE WEEKS VERSUS SIX WEEKS

We have demonstrated that a maximal exercise test six weeks after infarction is significantly better than a submaximal exercise test three weeks after infarction in identifying patients with multivessel disease (Fig. 3c, $p<0{\cdot}05$) and three vessel disease (Fig. 3b, $p<0{\cdot}05$), but not two vessel disease (Fig. 3c, p=NS). No patient with three vessel disease had a positive exercise test at three weeks that became negative at six weeks (Fig. 3b). Neither exercise test was highly sensitive or specific when the data were analysed on the basis of a significant reduction in luminal diameter being ≥50% or ≥70% (Table 3).

Several factors may explain the differences in results between this and previously published studies (Table 3). We studied consecutive patients who fulfilled no specific criteria except that they survived their acute myocardial infarction, agreed to participate in the study, and had no other serious noncardiac disease. Others, however, have studied selected study populations. They have included consecutive patients fulfilling specific criteria,[10 11] nonconsecutive patients with symptoms or an abnormal haemodynamic response to exercise,[8] or survivors of an uncomplicated myocardial infarction.[7 9 16] The age of the subjects investigated may also be important. Most previous studies, except that of Akhras *et al*,[7] have included older patients in whom the frequency of both previous myocardial infarction[8 9 19] (which has been associated with a higher prevalence of multivessel disease[3]) and multivessel disease[7 8 10] are higher (Table 3). The sensitivity of exercise testing might therefore be expected to be greater. Another important factor may be the exercise protocol used. Two previous studies have used a modified Bruce protocol to a submaximal end point at 2–3 weeks after infarction but in an older

| *ngiography* | | *Multivessel disease* | | | *Multivessel disease with negative tests* | *3 VD with negative tests* |
|---|---|---|---|---|---|---|
| *enosis* | *Multivessel disease* | *Sensitivity* | *Specificity* | *Predictive value* | | |
| )% | 74% | 96% | 94% | 98% | 12% | — |
| )% | 72% | 88% | 69% | 88% | 31% | — |
| )% | 50% | 65% | 90% | 87% | 28% | 29% |
| )% | 71% | 56% | 86% | 90% | 55% | 40% |
| )% | 69% | 58% | 83% | 74% | 64% | — |
| )% | 60% | 38% | 83% | 76% | 54% | 68% |
| )% | 48% | 46% | 77% | 65% | 39% | 67% |
| )% | 60% | 55% | 75% | 77% | 47% | 41% |
| )% | 48% | 65% | 73% | 69% | 31% | 33% |

group of patients.[9 10] Their figures for sensitivity in detecting multivessel disease were similar to those obtained at the maximal six week exercise test in our patients and similar numbers of patients with negative exercise tests had multivessel disease (Table 3).

It was difficult to understand the pronounced differences in results between this study and that of Akhras *et al* in patients of a similar age.[7] The major differences between the studies are the differing frequency of multivessel disease, their use of symptom limited exercise testing at 2–3 weeks after infarction, and their method of analysis which was based on ST segment changes only. This latter point may have little bearing on the differing results since heart rate limited and symptom limited exercise testing three weeks after infarction have been shown to have a similar yield of ST segment depression[22] although this was in different groups of patients. Use of such a method of analysis in the present study would have resulted in much poorer figures for sensitivity and specifity.

The results of the present study once again stress the importance of angina pectoris as a variable identifying patients with multivessel disease.[8] Multivessel disease was found in 74% of patients with a clinical history of angina six weeks after infarction, confirming the findings of Alijarde *et al*,[23] and in 90% of patients with exercise induced angina at the maximal six week exercise test.

As in previous studies[9–11] considerable numbers of patients with multivessel disease or three vessel disease had negative exercise tests. In view of recently published data these patients may represent a subgroup with a better prognosis than the extent of their coronary artery disease would suggest.[24]

We were unable to confirm previously published data suggesting a higher incidence of multivessel disease in patients with inferior infarction.[23 25] The frequency of multivessel disease in patients with anterior or inferior infarction did not differ significantly, thus confirming the findings of Veenbrink *et al*[14] and Roubin *et al*.[26]

## CONCLUSIONS

The present study demonstrates that early exercise testing after acute myocardial infarction in patients under 55 years is of limited value in predicting the extent of coronary artery disease. Precordial mapping offers no advantages over the standard 12 electrocardiogram leads in either the identification of patients with multivessel disease or in the prediction of the distribution of coronary artery disease. The symptom limited six week exercise test has been shown to identify significantly more patients with either multivessel disease ($p < 0{\cdot}05$) or three vessel disease ($p < 0{\cdot}05$) than the earlier submaximal test. Many patients with coronary artery disease known to have an adverse effect on prognosis are, however, not identified. We therefore suggest that it is unreasonable to use early exercise testing as a guide to the selection of patients for coronary arteriography after acute myocardial infarction.

Angina pectoris either as a presenting symptom early after infarction or when it occurs during exercise testing (with or without ST segment depression) is a strong predictor of multivessel disease. Because these patients may represent a high risk group for subsequent cardiac events we recommend coronary arteriography in this group.

I P was supported by the National Heart Research Fund and C A by Bayer Pharmaceuticals.

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# Abnormalities of the peripheral circulation and respiratory function in patients with severe heart failure

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SUMMARY To investigate the peripheral circulatory and respiratory abnormalities which occur in patients with heart failure, forearm and calf blood flow were measured before and after upright exercise, and respiratory gas exchange was measured during exercise in 26 patients with severe heart failure. Compared with a group of normal subjects the patients had reduced limb blood flow at rest and the response of limb blood flow to upright exercise was also abnormal. The increase in calf blood flow after exercise and the reduction in blood flow in the non-exercising forearm were both smaller in patients than in controls. There was a significant correlation between the maximum exercise duration of the patients and calf blood flow both after exercise and at rest. Compared with another group of control subjects the patients had a higher minute ventilation during exercise and a reduced oxygen consumption. The respiratory exchange ratio during exercise was also higher in patients than in controls. This suggests that there is early onset of anaerobic metabolism during exercise in patients with severe heart failure.

Severe heart failure is characterised by abnormalities in the peripheral circulation. Both arterial and venous vasoconstriction occur which ultimately may be detrimental to the performance of the failing myocardium. Attempts to correct these abnormalities provide the pathophysiological basis for the use of vasodilators in heart failure.[1] Monitoring of the central haemodynamic effects of vasodilators indicates that many agents have beneficial effects on myocardial performance.[2-4] There is now considerable evidence, however, that short term changes in central haemodynamics in response to vasodilator treatment do not correlate with symptomatic improvement as judged by changes in exercise tolerance.[5 6] We have previously shown that changes in the arteriolar tone of a vascular bed consisting predominantly of skeletal muscle correlate with changes in exercise tolerance in response to vasodilator treatment.[7] This suggests that an important effect of vasodilator treatment is to cause arteriolar vasodilatation in skeletal muscle and so improve oxygen delivery to that muscle during exercise.

Limb blood flow can be measured by simple non-invasive techniques. Previous reports have suggested that blood flow is reduced in the forearm, a vascular bed consisting predominantly of skeletal muscle, in patients with severe heart failure.[8] In addition the increase in blood flow in response to ischaemia and isometric exercise is attenuated compared with that in normal subjects.[8] Little is known, however, about the effect of upright exercise on limb blood flow. To investigate the response to upright exercise we have made simultaneous measurements of forearm and calf blood flow before and after exercise in a group of patients with severe heart failure.

Patients with heart failure have a reduced maximal oxygen consumption during exercise, and blood lactate concentrations indicate that the onset of anaerobic metabolism in exercise occurs earlier than it does in normal subjects.[9 10] This implies that oxygen consumption may be below normal during submaximal exercise. To investigate this possibility we have measured oxygen uptake, respiratory exchange ratio, and minute ventilation during exercise and have compared the results obtained with those from a group of normal subjects.

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Accepted for publication 14 September 1985

## Patients and methods

### PATIENTS

Twenty six patients aged 46–69 years were studied; 24 were male. All were limited on exertion by fatigue or dyspnoea or both despite taking at least 80 mg of frusemide daily. Heart failure was due to ischaemic heart disease in 19 of the patients and to dilated cardiomyopathy in the remaining seven. All had been on stable treatment for at least four weeks before being studied and none was taking a vasodilator.

### EXERCISE TESTING

At each visit the patients were exercised on a treadmill to a symptom limited maximum. The speed and slope of the treadmill was increased after three minutes at each of the following stages given as kph and slope in degrees; I, 2·7 and 0; II, 2·7 and 1·3; III, 2·7 and 2·6; IV, 2·7 and 4·0; V, 4·0 and 5·6; VI, 5·4 and 6·2; VII, 6·8 and 7·2.

To overcome changes which may have occurred due to familiarisation with the exercise protocol and with the method used to measure respiratory gases each patient was exercised on consecutive weekly visits until their symptom limited exercise time at two consecutive visits did not increase by more than 5%. This last exercise test was taken to represent the maximum exercise tolerance of the patient, and the measurements of limb blood flow and respiratory function made on that occasion were those that are used in this report.

### RESPIRATORY GAS ANALYSIS

During each symptom limited exercise test oxygen uptake, respiratory exchange ratio, and ventilation were measured every minute with an online gas analyser (PK Morgan).

### MEASUREMENT OF LIMB BLOOD FLOW

Initial measurements of limb blood flow were made before the symptom limited exercise test, and after this exercise test each patient was rested in a temperature controlled room (22–24°C) for one hour. By this time limb blood flow had returned to preexercise values. Each patient then underwent a second, submaximal, exercise test. A submaximal test was used to determine the effects of exercise on limb blood flow for two reasons. First to enable us to measure the highest oxygen consumption of the patients during the symptom limited test, and second to eliminate movement artefacts from the recordings caused by the excessive ventilatory effort of maximal exercise. The duration of the submaximal test was determined by the patients' performance during the maximal test. Each patient was asked to exercise to achieve a workload that in the symptom limited test required an oxygen consumption of 12 ml/kg/minute. If the patient failed to achieve this oxygen consumption during the symptom limited test the submaximal test was terminated at the end of the exercise stage before the one in which they became symptom limited. This level of workload was chosen because it represented a moderate degree of exercise for most of the patients and experience had shown that it produced substantial changes in limb blood flow in normal controls.

Simultaneous measurements of forearm and calf blood flow were made in the right forearm and calf by venous occlusion plethysmography using mercury-in-silastic strain gauges.[11] In brief, the technique consists of measuring the rate of change of limb volume, which is determined by limb blood flow, in response to intermittent venous occlusion. Limb blood flow was measured at rest and every minute from three to 13 minutes after submaximal exercise. The right arm was held loosely at the side during the submaximal exercise test.

### CONTROL SUBJECTS

Two groups of normal subjects without signs or symptoms of cardiovascular disease were used as controls. All the subjects were male. The age range was similar in patients and controls. Eighteen subjects were exercised to the end of stage IV of the protocol during which measurements of oxygen consumption, respiratory exchange ratio, and ventilation were made. Seventeen subjects in a second group were exercised to establish a workload that required an oxygen consumption of 12 ml/kg/minute. After one hour's rest forearm and calf blood flow measurements were made at rest and 3–13 minutes after exercise to this workload.

### STATISTICAL ANALYSIS

Analysis of variance for repeated measures was used to compare changes in limb flow between the patients and controls. We used *t* tests to compare differences in respiratory function during exercise between the patients and the controls, during which the patient number varied. Comparison of calf blood flow with maximum exercise time was performed with Pearson's moment correlation coefficient.

## Results

The mean maximum exercise time for the group of patients was 10·47 minutes (range 1·2–17·5 minutes) and the mean highest oxygen consumption was 12·5 ml/kg/minute (range 5·8–25·2 ml/kg/minute).

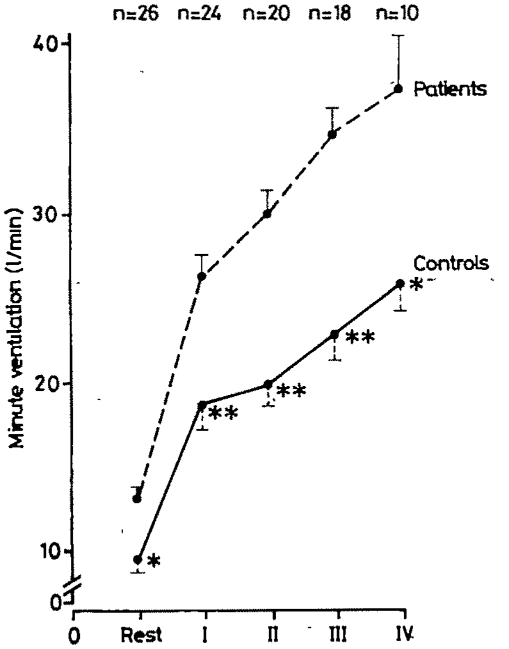

Fig. 1 *Mean (SEM) values of minute ventilation at rest and during stages I–IV of the exercise protocol for patients and controls.* $^{*}p<0{\cdot}05$, $^{**}p<0{\cdot}005$.

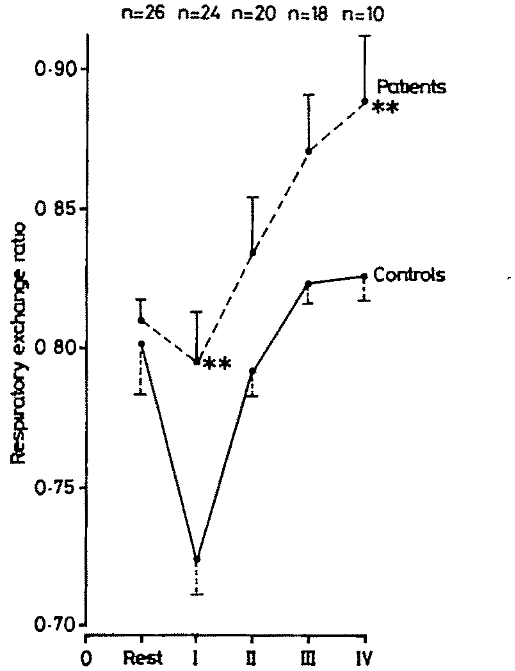

Fig. 3 *Mean (SEM) values of respiratory exchange ratio at rest and during stages I–IV of the exercise protocol for patients and controls.* $^{**}p<0{\cdot}05$.

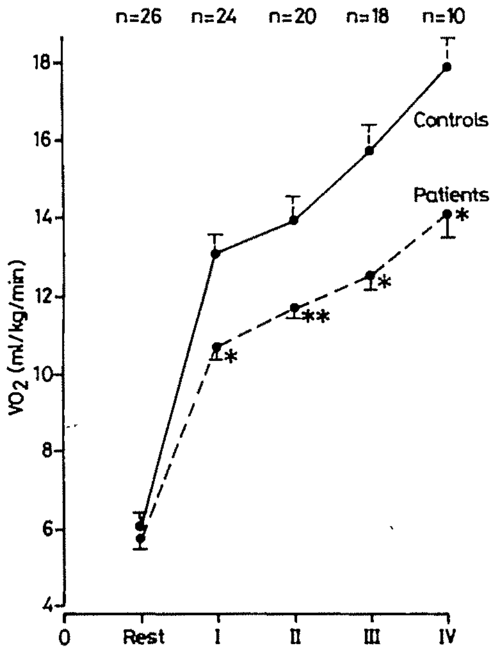

Fig. 2 *Mean (SEM) values of oxygen uptake at rest and during stages I–IV of the exercise protocol in patients and controls.* $^{*}p<0{\cdot}03$, $^{**}p<0{\cdot}02$.

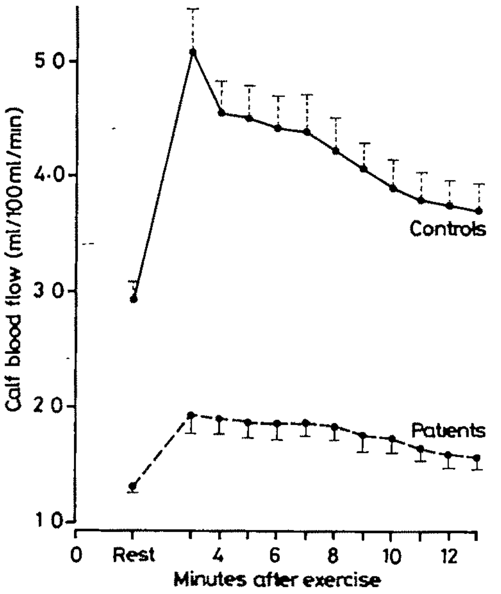

Fig. 4 *Mean (SEM) values of calf blood flow at rest and from 3–13 minutes after submaximal exercise for the patients and controls.* $p<0{\cdot}001$.

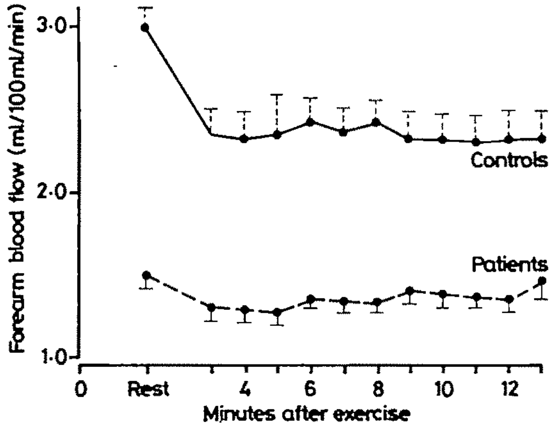

Fig. 5 *Mean (SEM) values of forearm blood flow at rest and from 3–13 minutes after submaximal exercise in patients and controls.* $p<0{\cdot}001$.

## MEASUREMENTS OF RESPIRATORY FUNCTION

Fig. 1 shows the mean (SEM) values of minute ventilation during exercise for the patients and controls. Twenty six patients had resting measurements made, 24 patients completed stage I of the exercise protocol, 20 completed stage II, 18 completed stage III, and 10 completed stage IV. The patients had higher values for minute ventilation both at rest and during exercise than the controls ($p<0{\cdot}05$ at rest, $p<0{\cdot}005$ at stage I, $p<0{\cdot}005$ at stage II, $p<0{\cdot}005$ at stage, III, and $p<0{\cdot}05$ at stage IV).

Fig. 2 shows the effects of exercise on the mean (SEM) values of oxygen uptake in the patients and the control subjects. Oxygen consumption was not significantly different between the patients and the control subjects at rest. As exercise progressed there was the expected increase in oxygen consumption in both groups but the patients consistently showed a lower oxygen consumption than the control subjects ($p<0{\cdot}03$ at stage I, $p<0{\cdot}02$ at stage II, $p<0{\cdot}03$ at stage III, and $p<0{\cdot}03$ at stage IV).

Fig. 3 shows the values for respiratory exchange ratio for the patients and the control subjects. There was no difference between the groups at rest; however, as exercise progressed the patients showed a

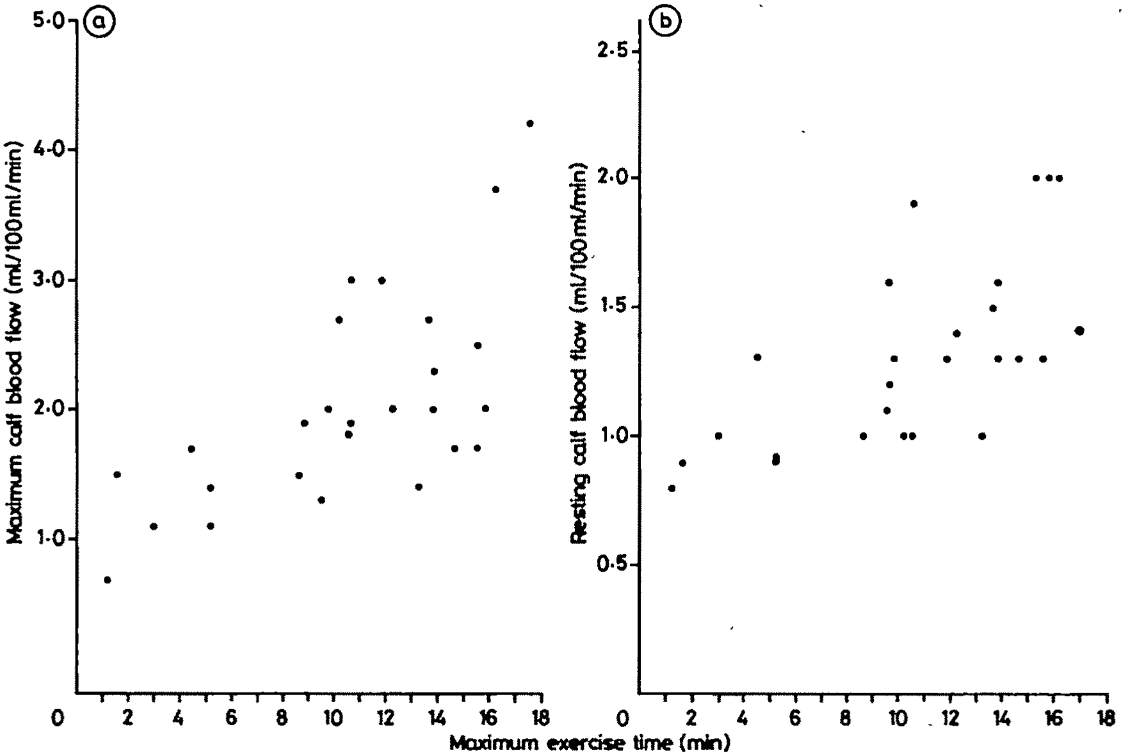

Fig. 6 *(a) Relation between maximum exercise time and maximum value of calf blood flow after submaximal exercise in patients.* $r=0{\cdot}642$, $p<0{\cdot}01$. *(b) Relation between maximum exercise time and resting calf blood flow in patients.* $r=0{\cdot}526$, $p<0{\cdot}02$.

higher respiratory exchange ratio than the control subjects ($p < 0\cdot05$ at stage I and stage IV).

### MEASUREMENTS OF LIMB BLOOD FLOW

The mean (SEM) oxygen consumption of the patients at the end of the submaximal exercise test was 11·6 (±0·58) ml/kg/min. Fig. 4 shows the resting and post-exercise values of calf blood flow for the patients and the control subjects. The mean (SEM) value of resting calf blood flow in the control subjects was 2·98 (±0·14) ml/dl/min, whereas in the patients it was 1·32 (±0·07) ml/100 ml/min. After submaximal exercise calf blood flow had increased in the control subjects to a peak of 5 07 (±0·39) ml/100 ml/min. Peak calf blood flow after exercise in the patients was 1·93 (±0·17) ml/100 ml/min. The patients, therefore, not only had reduced calf blood flow at rest but also had an attenuated vasodilator response to similar degrees of exercise ($p < 0\cdot001$).

Fig. 5 shows the effect of exercise on blood flow in the non-exercising forearm. The mean (SEM) resting value for the control subjects was 2·98 (±0·12) ml/100 ml/min compared with a resting value for the patients of 1·51 (±0·09) ml/100 ml/min. After exercise, forearm blood flow in the controls fell to 2·35 (±0·14) ml/100 ml/min three minutes after exercise. The corresponding value in the patients was 1·30 (±0·07) ml/100 ml/min. The reduction in blood flow in the forearm after exercise was therefore considerably smaller in the patients ($p < 0\cdot001$).

Fig. 6a shows the relation between maximum exercise time and the maximum value of calf blood flow achieved after submaximal exercise for each patient. There was a significant positive correlation between these variables, $r = 0\cdot642$ ($p < 0\cdot01$). Resting values of calf blood flow and maximum exercise time were also positively correlated, $r = 0\ 526$ ($p < 0\cdot02$, Fig. 6b).

## Discussion

This study has shown that patients with severe heart failure who remain symptomatic despite diuretic treatment have abnormalities of limb blood flow and of respiratory gas exchange. Since one of the predominant symptoms of patients with severe heart failure is dyspnoea it is not surprising that the patients had a higher minute ventilation, both at rest and during exercise, than the controls.

The differences in oxygen consumption are, however, more surprising. There was no difference in oxygen consumption between the patients and the controls at rest, but oxygen consumption was consistently lower in the patients during exercise. This observation does not accord with some published reports.[12 13] Franciosa *et al* have suggested that oxygen consumption during submaximal exercise is the same in patients with heart failure as normal controls.[12] Six of their patients, however, had a "normal" exercise capacity with a maximal oxygen consumption of greater than 20 ml/kg/minute, whereas only one of our patients had a maximal oxygen consumption as high as this. Furthermore the maximal oxygen consumption of many of their patients was greater than that in our patients. Similarly 12 of the patients studied by Patterson *et al* had a mean maximal oxygen consumption of 32·5 ml/kg/min.[13] The inclusion of these patients in the comparison of oxygen consumption during submaximal exercise with normal controls may well have hidden a reduction in oxygen consumption in the patients with more severe heart failure. Wilson *et al* measured oxygen consumption during submaximal exercise in patients with varying degrees of heart failure and showed a non-significant trend towards a lower systemic oxygen consumption during submaximal exercise in patients with more severe heart failure.[14]

The higher respiratory exchange ratio for the patients during exercise is consistent with the lower oxygen consumption and indicates the early onset of anaerobic metabolism.

The results described here are supported by studies which evaluated the metabolic consequences of exercise in the limbs in patients with heart failure. Patients with severe heart failure have a lower oxygen consumption in the forearm than controls in response to submaximal exercise.[15 16] In addition differences in the forearm skeletal muscle metabolism between patients and control subjects have been reported in a nuclear magnetic resonance study.[17] These data suggest that there is a reduction in oxygen consumption in skeletal muscle during submaximal exercise in patients with heart failure; this must be reflected in a reduction of systemic oxygen consumption, as we have demonstrated.

The differences in limb blood flow between the patients and controls may explain the differences in oxygen consumption. Patients with heart failure are capable of a greater oxygen extraction than controls.[16] This compensatory mechanism may, however, be insufficient to prevent the early onset of anaerobic metabolism if blood flow to exercising muscle is severely reduced. This study has demonstrated that both forearm and calf blood flow are reduced at rest in patients with heart failure. Although the technique we used to measure limb blood flow does not permit us to make measurements during exercise, the changes that occurred after exercise allow us to make some assumptions about changes during exercise. The increase in calf blood flow after exercise was considerably attenuated in the patients compared with that in the controls and, therefore, it is highly likely that calf blood flow, and hence oxygen delivery to the exercising skeletal muscle, was reduced during exercise. The changes in limb blood flow in the non-exercising forearm indicate that the resistance vessels in the forearm were near maximally constricted at rest and were unable to constrict further during exercise to aid redistribution of blood to the exercising limb.

The relation between resting and post-exercise calf blood flow and maximum exercise capacity of the patients indicates that limb blood flow is a major determinant of exercise tolerance in patients with severe heart failure. Since fatigue on exertion is also a major symptom of patients and is due to lactate accumulation in skeletal muscle and the associated intracellular acidosis,[14] the extent of the reduction in blood flow would determine the onset of these changes during exercise. Using different techniques others have also suggested that reduced limb blood flow is an important cause of the reduced exercise tolerance of patients with severe heart failure.[14]

The reduced blood flow to exercising skeletal muscle would also account for the lack of immediate improvement in exercise tolerance in patients treated with vasodilators, despite immediate improvement in central haemodynamics. It has been shown that in the short term captopril improves central haemodynamics without affecting exercise time.[6] We and others have demonstrated that short term administration of captopril does not affect limb blood flow and it is only after more prolonged administration that limb blood flow improves.[7 18] Thus the improvement in exercise time seems to be related more to the improved blood flow to skeletal muscle than to central haemodynamic effects.

Comparison of the changes in the peripheral circulation and respiratory gas exchange in patients with severe heart failure with those in normal subjects indicates some of the important pathophysiological changes that occur in patients with heart failure. The techniques used in this study are non-invasive and readily repeatable and may therefore be used to assess the response of patients to treatment.

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*Br Heart J* 1986; 55: 81–91

# Diagnostic and surgical management of patients with aneurysms of the thoracic aorta with various causes

## *Echocardiography and contrast enhanced computed tomography in prophylactic replacement of the ascending aorta*

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SUMMARY Sixty eight patients with aneurysms of the thoracic aorta were studied. Forty one had aortic dissection, 24 had dilatation only, and three had transverse aortic rupture. Sixteen had Marfan's syndrome; 17 had hypertension; and in eight there were other causal factors. In 17 the cause of the aneurysm was unknown. Histological examination did not help to establish the cause of aneurysm. Echocardiography failed to detect dissection of the ascending aorta in four (21%) out of 19 cases studied.

The mortality rate in the whole series was 26%. Early (operative and hospital) and late deaths occurred in 20% and 6% of patients respectively. The early mortality rate was 40% in the 24 emergency cases of dissection of the ascending aorta, 9% in patients operated on for dilatation of the ascending and transverse aorta without dissection, and 8% in patients with chronic dissection of the ascending aorta who had elective operation. Early and late mortality rates were no higher in patients with Marfan's disease than in any of the other groups.

It is suggested that contrast enhanced computed tomography should be performed in all patients with pronounced aortic root dilatation and in patients with Marfan's disease with symptoms which suggest dissection, even if they have only slight aortic root dilatation. Preventive replacement of the ascending aorta should be considered in more patients to reduce the number of emergency operations, in which the mortality rate is high. There is no definite limit of aortic root dilatation above which preventive replacement of the ascending aorta should be routinely considered.

Angiography and echocardiography have greatly increased the accuracy of diagnosis of aneurysms of the thoracic aorta. Surgery is now the preferred treatment for aneurysms, especially for those of the ascending aorta. New methods of investigation will improve knowledge of the anatomy of these lesions and may lead to improvement in their management.

We report the results of surgery in 68 patients with aortic aneurysm, together with the value of echocardiography and contrast enhanced computed tomography in managing these patients.

## Patients and methods

We studied 68 consecutive patients operated on between January 1979 and December 1982. There were 54 men, mean (SD) age 47·6 (13·3) years (range 14–69) and 14 women, mean age 42·6 (13·3) years (range 21–65). Twenty seven had acute symptoms and 41 had chronic symptoms which suggested aortic lesions.

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Accepted for publication 21 May 1985

### SKELETAL AND OPHTHALMOLOGICAL EVALUATIONS

Skeletal abnormalities were assessed by the metacarpal index (normal values under 8·4) and the difference between height and arm span (normal values <7·6 cm).[1] Patients with subluxation of the lenses and abnormalities of the anterior chamber angle were classified as probable (+ +) or possible (+) cases of Marfan's syndrome.[2]

### CARDIOVASCULAR EVALUATION

*Echocardiography*—M mode and cross sectional echocardiograms were recorded before operation in 36 patients who were examined for the presence of the following conditions: aortic root dilatation by criteria suggested by Brown *et al*[3]; aortic root dissection, and mitral valve prolapse. Serial studies were possible preoperatively in 13 patients with chronic lesions of the aorta (with at least three examinations at intervals of six months) and in 10 of them contrast enhanced computed tomography was performed. Increases of more than 10% of the aortic root diameter measurement were regarded as important.

*Angiography*—Aortography and left ventricular angiography with selective coronary arteriography were performed in all patients with dilatation of the ascending aorta, and in those in whom dissection of the ascending aorta was suspected. Aortography alone was performed in patients with dissection of the descending aorta. We defined aortic dissections as type I, II, III, according to De Bakey's classification. Severity of aortic valve and mitral valve regurgitation was assessed by angiography on a scale of 1 to 4. Grades 3 and 4 indicated severe regurgitation. Angiography was performed after operation in eight cases in which dissection extended from the ascending aorta into the arch and beyond (type I); in two with dissection only of the ascending aorta (type II); and in three with dissection of the descending tract of the thoracic aorta (type III).

*Contrast enhanced computed tomography* was performed before operation in 10 patients in whom dilatation of the ascending aorta had been diagnosed by echocardiography and after operation in 17 patients (11 operated on for type I dissections, three for type II, two for type III, and one for rupture of the transverse aorta). Both angiography and contrast enhanced computed tomography were performed postoperatively in five patients, four of whom has been operated on for type I dissections. Contrast enhanced computed tomography was performed with a Siemens Somaton 2 at a scan speed of 3·5 seconds after multiple rapid peripheral intravenous injections of 25–50 ml of Urografin (Schering) up to a maximum of 200 ml.

### SURGICAL TREATMENT

In the absence of contraindications, medical treatment (antihypertensive and negative inotropic agents) was given in the first hours after admission to hospital and during angiography in an attempt to stabilise the patient's condition. An operation was considered immediately if medical treatment was contraindicated or when, despite medical treatment, there was rapid deterioration of the patient's haemodynamic state or persistent pain suggestive of progressive dissection.

For aneurysms of the ascending aorta and in type I and type II dissections the tract of affected aorta was replaced through a median sternotomy by a low porosity Dacron graft with or without reimplantation of the coronary arteries. In patients with severe aortic regurgitation and aneurysms or dissections, a composite graft with a valve prosthesis (Sorin) was used except in three patients with dilatation of ascending aorta and severe aortic regurgitation in whom a valve prosthesis and a vascular prosthesis were implanted. In cases of dissection the false channel was obliterated and the two layers affected by the dissecting process were cuffed proximally and distally with Teflon.

The dilatations and dissections of the descending thoracic aorta were approached through a posterolateral thoracotomy, with cannulation of the left femoral vein and artery for partial bypass to perfuse the legs during cross clamping.

For cerebral protection we used moderate hypothermia (25°C) during operations on aneurysms and type II and III dissections and profound hypothermia (15°C) in type I dissections.[4] In profound hypothermia cooling and rewarming times increased with the patient's body surface area. A cardioplegic solution was introduced directly into the coronary ostia and pericardial ice slush was used to produce local cardiac cooling.

The sections of aorta removed at operation were examined to determine the severity of cystic medial necrosis, elastin fragmentation, fibrosis, and medionecrosis, and compared with those of 30 normotensive subjects of similar age.

Late follow up of survivors ranged from 24 months to six years (mean 47 months).

### DEFINITIONS

Patients were described as having Marfan's syndrome if they had typical abnormalities of at least two of the three organ systems evaluated; they were described as having formes frustes if, together with the aortic abnormalities, one only of the two assess-

Table 1 *Clinical diagnosis of the thoracic aortic lesions*

| | *Male patients* | *Female patients* | *Total, mean (SD) age, and age range (yr)* |
|---|---|---|---|
| No of patients | 54 | 14 | 68 |
| Acute dissection | 21 | 3 | 24<br>44·7 (12·1)<br>19–65 |
| Chronic dissection | 15 | 2 | 17<br>54·3 (9·8)<br>27–68 |
| Type I | 20 | 4 | 24<br>45·1 (11·4)<br>21–65 |
| Type II | 10 | | 10<br>52·3 (13·6)<br>19–68 |
| Type III | 6 | 1 | 7<br>56·0 (8·0)<br>42–64 |
| Rupture of the transverse aorta | 1 | 2 | 3<br>14–40 |
| Aneurysm without dissection | 17 | 7 | 24<br>45·7 (13·0)<br>29–69 |
| Aneurysm of the ascending aorta | 13 | 2 | 15<br>44·7 (12·7)<br>29–65 |
| Aneurysm of the transverse aorta | 2 | 5 | 7<br>43·3 (12·6)<br>29–62 |
| Aneurysm of the descending aorta | 2 | | |

ments for skeletal evaluation was abnormal or both showed values at the upper limits, or if there were moderate alterations of the anterior ocular chamber angle.

Patients were deemed to have hypertension if there was a history of drug treatment for diastolic hypertension or if their diastolic pressure was higher than 99 mm Hg.

Trauma, aortic valve stenosis, aortic valve prosthesis, bicuspid aortic valve, and coarctation of the aorta were regarded as other causal factors; but a possible association with Marfan's syndrome, or hypertension was always considered.[5–7]

When none of the conditions described above was present the aneurysm was described as being of unknown cause. We subdivided patients into four groups on the basis of these definitions.

## Results

### CARDIOVASCULAR EVALUATION

Table 1 shows the clinical diagnoses of the 68 patients.

### AETIOLOGICAL AND ANATOMICAL FINDINGS

*Lesions in patients with connective tissue disease*

Skeletal, ophthalmological, and cardiovascular examinations led to the diagnosis of connective tissue disease in 16 patients. Ten had typical Marfan's syndrome and six had formes frustes of Marfan's syndrome. Type I dissections were seen in five patients with typical features of Marfan's sydrome and in three with formes frustes (Table 2). In four other cases with typical features and in two with formes frustes there was dilatation of the ascending aorta (Table 3); in one woman with formes fruste and history of a recent trauma, there was dilatation of the transverse aorta (case 44). Emergency operations were performed in five subjects with type I dissections and in one boy with rupture of the transverse aorta. All six had features typical of Marfan's syndrome. In the boy with rupture of the transverse aorta, the metacarpal index was 9·1, there were ocular abnormalities, and mitral valve prolapse (without dilatation of the aortic root) was present. Mitral valve prolapse was observed in three of the 16 patients. They all had aortic dilatation, except the boy with rupture of the transverse aorta and the woman with dilatation of the transverse aorta.

*Lesions in patients with hypertension*

Aortic dissection was seen in 19 hypertensive patients; type I in eight, type II in five, and type III in six (Table 2). Dilatation of the ascending aorta was seen in four patients, of the transverse aorta in one, and of the descending aorta in two (Table 3). Ten had emergency operations.

*Lesions in patients with aneurysms and other causal factors*

Traumatic rupture of the transverse aorta was seen in two women, one with diastolic hypertension; traumatic dilatation of the unruptured aorta was seen in two other women (cases 42 and 44), one of whom had an abnormal metacarpal index and a mitral valve prolapse (Table 3). A congenital bicuspid aortic valve was seen in one man with type II chronic dissection and hypertension (case 28) and in one man with dilatation of the ascending aorta and Marfan's syndrome (case 49). There was coarctation of the aorta in a boy with type II acute dissection (case 4) and in a woman with dilatation of the transverse aorta (case 45). In one man (case 37) with aortic valve stenosis and type II chronic dissection there was an abnormal height-arm span difference; in three other men who had had an aortic valve replaced, there were type I dissections in two (cases 15 and 35) and dilatation of only the ascending aorta in one (case 51).

Table 2 *Skeletal, ophthalmological, and cardiovascular examination in patients with acute or chronic aortic dissection**

| *Case No* | *Sex* | *Age (yr)* | *Evidence for inheritance of Marfan's syndrome* | *Height-span difference (cm)* | *Metacarpal index* | *Ocular evidence of Marfan's syndrome* | *Hypertension* | *Trauma* | *Echocardiography* | *Angiography* | *Remarks* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Acute dissection:* | | | | | | | | | | | |
| 1 | F | 33 | No | −2 | 8·4 | + | No | No | Dilatation | Type I | Marfan's syndrome |
| 2 | F | 41 | | | | | | No | | Type I, MVP | Unknown cause† |
| 3 | F | 47 | | | | | | No | Dissection | Type I | Unknown cause† |
| 4 | M | 19 | | | | | | No | | Type II, SAR, coarctation of the aorta | Other cause† |
| 5 | M | 21 | Yes | −6 | 8·6 | ++ | No | No | Dissection | Type I, SAR | Marfan's syndrome |
| 6 | M | 30 | No | −7·6 | 8·7 | No | No | No | Dissection | Type I, SAR | Marfan's syndrome |
| 7 | M | 30 | No | −7·5 | 9·0 | No | No | No | Dissection | Type I | Marfan's syndrome |
| 8 | M | 40 | No | 3 | 7·9 | No | Yes | No | | Type I | Hypertension |
| 9 | M | 42 | No | −2 | 8·6 | No | No | No | Dissection, MVP | Type I, MVP | Marfan's syndrome |
| 10 | M | 42 | | | | | | No | Dilatation | Type I, SAR | Unknown cause† |
| 11 | M | 42 | | | | | Yes | No | Dissection | Type I, SAR | Hypertension† |
| 12 | M | 42 | | | | | Yes | No | | Type III | Hypertension |
| 13 | M | 42 | No | −5 | 7·8 | No | No | No | Dissection | Type I | Unknown cause |
| 14 | M | 47 | | | | | | No | Dissection | Type I | Unknown cause |
| 15 | M | 47 | | | | | | No | | Type I, SAR | Other cause‡ aortic valve replacement |
| 16 | M | 49 | | | | | Yes | No | | Type II | Hypertension |
| 17 | M | 50 | | | | | Yes | No | | Type I | Hypertension† |
| 18 | M | 51 | No | −11 | | No | No | No | | Type II, SAR | Unknown cause |
| 19 | M | 55 | No | −6·5 | 7·9 | No | Yes | No | Dissection | Type I | Hypertension |
| 20 | M | 56 | No | −6 | 7·8 | No | Yes | No | Dissection | Type I | Hypertension |
| 21 | M | 59 | | | | | Yes | No | | Type II | Hypertension† |
| 22 | M | 61 | | | | | Yes | No | Dissection | Type I | Hypertension† |
| 23 | M | 62 | | | | | Yes | No | | Type III | Hypertension† |
| 24 | M | 65 | | | | | | No | | Type I | Unknown cause† |
| *Chronic dissection:* | | | | | | | | | | | |
| 25 | F | 52 | | | | | Yes | No | | Type I | Hypertension |
| 26 | F | 62 | No | −2 | 7·2 | No | Yes | No | | Type III | Hypertension |
| 27 | M | 27 | No | −8 | 11 | No | No | No | Dilatation | Type I, SAR | Marfan's syndrome‡ |
| 28 | M | 46 | No | −5 | 7·2 | No | Yes | No | | Type II, bicuspid aortic valve | Hypertension |
| 29 | M | 46 | No | 1 | 8·8 | No | No | No | Dissection | Type I | Marfan's syndrome |
| 30 | M | 47 | No | −7·5 | 8·8 | No | No | No | Dilatation | Type I, SAR | Marfan's syndrome |
| 31 | M | 50 | | | | | Yes | No | | Type III | Hypertension |
| 32 | M | 51 | | −1 | 7·9 | | No | No | | Type II, SAR | Unknown cause |
| 33 | M | 53 | No | 5 | | No | Yes | No | | Type III | Hypertension |
| 34 | M | 56 | | | | | No | No | | Type II | Unknown cause |
| 35 | M | 56 | | | | | No | No | Dissection | Type I | Other cause† aortic valve replacement |
| 36 | M | 59 | No | −5·5 | 8·15 | No | No | No | | Type III | Unknown cause |
| 37 | M | 59 | No | −8 | 7·85 | No | No | No | | Type II | Other cause stenosis of aortic valve |
| 38 | M | 63 | No | −6 | | No | Yes | No | Dissection | Type I | Hypertension |
| 39 | M | 64 | | | | | Yes | | | Type III | Hypertension† |
| 40 | M | 65 | | | | | Yes | | | Type II, SAR | Hypertension |
| 41 | M | 68 | No | | | No | Yes | No | Dissection | Type II | Hypertension |

*Three cases, including a boy with Marfan's syndrome, with rupture of the transverse aorta are not presented in the Table.
Cases 1, 9, and 29 have formes frustes of Marfan's syndrome
Ocular evidence of Marfan's syndrome ++ probable, + possible.
†Early (operative and hospital) death; ‡late death.
MVP, mitral valve prolapse; SAR, severe aortic regurgitation (slight aortic regurgitation, if present, is not mentioned); dilatation, aortic root dilatation; dissection, aortic dissection.

*Lesions in patients with aneurysms of unknown cause*
Acute dissection of the ascending aorta was seen in seven patients and chronic dissection of the ascending aorta in three (Table 2). There was dilatation of the ascending aorta in three cases and dilatation of the transverse aorta in another three (Table 3). Mitral valve prolapse was observed in one woman at left ventricular angiography (case 2).

### HISTOLOGICAL FINDINGS

The severity of cystic medial necrosis (graded as 1 to 4, according to the amount of basophilic ground

Table 3 *Skeletal, ophthalmological, and cardiovascular evaluation in patients with aneurysm without dissection*

| *Case No* | *Sex* | *Age (yr)* | *Evidence for inheritance of Marfan's syndrome* | *Height-span difference (cm)* | *Metacarpal index* | *Ocular evidence of Marfan's syndrome* | *Hypertension* | *Trauma* | *Echocardiography* | *Angiography* | *Remarks* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 42 | F | 29 | | | | | | Yes | | TAA | Other cause |
| 43 | F | 32 | | | | | | No | | TAA | Unknown cause |
| 44 | F | 36 | No | −2 | 9·5 | No | No | Yes | MVP | TAA, MVP | Marfan's syndrome and trauma |
| 45 | F | 38 | | | | | No | No | | TAA, coarctation of aorta | Other cause‡ |
| 46 | F | 39 | | | | | No | No | | TAA | Unknown cause |
| 47 | F | 62 | No | −3 | 7·4 | No | Yes | No | | TAA | Hypertension |
| 48 | F | 65 | | | | | Yes | No | | AAA, SAR | Hypertension† |
| 49 | M | 29 | Yes | −6 | 7·3 | + + | No | No | Dilatation | AAA, SAR, bicuspid valve | Marfan's syndrome |
| 50 | M | 31 | No | −6 | 8·1 | No | No | No | Dilatation | AAA, SAR | Marfan's syndrome |
| 51 | M | 32 | No | 3 | 7·9 | No | No | No | Dilatation | AAA, SAR | Other cause aortic valve replacement |
| 52 | M | 33 | Yes | −7·5 | 8·8 | + + | No | No | Dilatation | AAA, SAR | Marfan's syndrome |
| 53 | M | 34 | No | −8 | 8·4 | No | No | No | Dilatation | AAA, SAR | Marfan's syndrome |
| 54 | M | 41 | No | −5 | 8·4 | + + | No | No | Dilatation | AAA, SAR | Marfan's syndrome |
| 55 | M | 41 | No | −4 | 8·4 | No | No | No | Dilatation | AAA, SAR | Marfan's syndrome |
| 56 | M | 42 | | | | | | No | Dilatation | AAA, SAR | Unknown cause‡ |
| 57 | M | 45 | | | | | Yes | No | Dissection | AAA, SAR | Hypertension |
| 58 | M | 51 | | | | | No | Yes | Dilatation | AAA | Other cause |
| 59 | M | 54 | No | −1 | 7·0 | No | Yes | No | Dilatation | DAA, AAA | Hypertension |
| 60 | M | 54 | | | | | Yes | No | Dilatation | AAA | Hypertension |
| 61 | M | 55 | No | −7 | 7·1 | No | No | No | | TAA | Unknown cause |
| 62 | M | 58 | | | | | No | No | Dilatation | AAA | Unknown cause† |
| 63 | M | 63 | No | −7 | 7·5 | No | No | No | Dilatation | AAA, SAR | Unknown cause |
| 64 | M | 63 | | | | | Yes | No | Dilatation | AAA | Hypertension |
| 65 | M | 69 | | | | | Yes | No | | DAA | Hypertension |

Cases 44, 50, and 55 had formes frustes of Marfan's syndrome.
Ocular evidence of Marfan's syndrome: + + probable.
†Early (operative and hospital) death; ‡late death.
Dilatation, aortic root dilatation; MVP, mitral valve prolapse; AAA, ascending aortic aneurysm; TAA, transverse aortic aneurysm; DAA, descending aortic aneurysm; SAR, severe aortic regurgitation.

substance and fragmentation of the elastic tissue) and the other histological findings were not significantly different in patients with aneurysm of unknown cause and in 30 normotensive subjects of similar age. There was no difference between patients with aneurysm and hypertension and the group of controls.

The degree of cystic medial necrosis in Marfan's syndrome was very variable and, in some cases, histological lesions were minimal.

### ECHOCARDIOGRAPHIC FINDINGS

Echocardiography was performed in 19 consecutive patients in whom ascending aortic dissections was diagnosed by angiography (Table 2). Cross sectional echocardiography detected aortic root dissection in 15 patients and M mode echocardiography detected dissection in nine. In four patients M mode and cross sectional echocardiography did not show aortic root dissection (Fig. 1). Echocardiography was also performed in 16 patients in whom aneurysms without dissection (Table 3) were diagnosed by angiography. In 14 of these, dilatation of the aortic root was detected (Fig. 2) and in nine there were signs of aortic root dilatation together with aortic valve regurgitation. In one patient (case 59), in whom aortic root diameter was moderately dilated, angiography showed a large aneurysm of the thoracic descending aorta that had been undetected by cross sectional echocardiography. In a woman with angio-

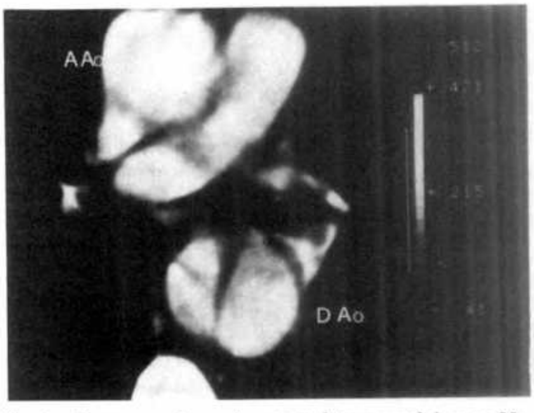

Fig. 1 *Contrast enhanced computed tomograph in case 30, showing type I aortic dissection. This lesion was not detected by echocardiography. AAo, ascending aorta; DAo, descending aorta.*

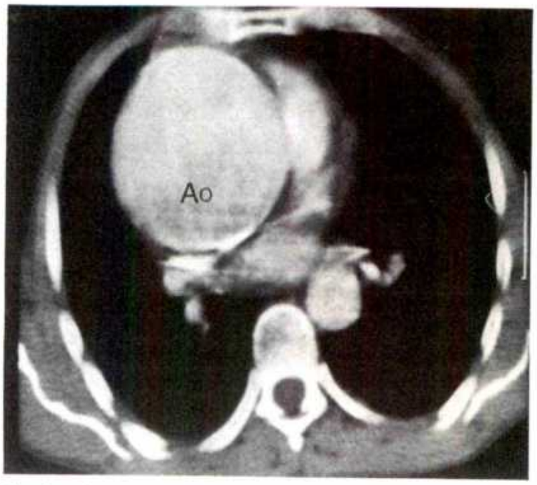

Fig. 2 *A contrast enhanced computed tomograph in case 60 confirming the results of an echocardiogram which showed severe aneurysm of ascending aorta and excluded dissection. Aortic calcifications are evident. Ao, aorta.*

graphic evidence of dilatation of the transverse aorta (case 44), echocardiography showed mitral valve prolapse but not the aortic dilatation. In a patient (case 57) dissection of the transverse aorta was incorrectly diagnosed (Fig. 3); however, in this subject ascending aortic aneurysm and aortic valve regurgitation were recognised by echocardiography.

In all patients aortic dilatation appeared to be symmetrical at M mode echocardiography and the precise location and extent of the aneurysm could not be detected. Identification of the aortic sinuses by cross sectional echocardiography enabled us to discern the site of the aneurysm or at least its starting point. We saw symmetrical dilatation beginning in the aortic sinus area in patients with Marfan's syndrome; this was distinct from the asymmetrical dilatation (often with saccular distortion) that was caused by other factors.

The diameter of the aortic root ranged between 50 and 86 mm by cross sectional echocardiography and measurements were slightly greater than those found at M mode echocardiography.

Echocardiography was performed only in one of the three cases with rupture of the transverse aorta. In this case—a boy with Marfan's syndrome—the rupture was not recognised.

Preoperative serial studies showed an important increase in aortic root diameter in 11 of the 13 cases. In the remaining two cases, in which contrast enhanced computed tomography diagnosed dissection, echocardiography did not show dissection or any increase of the aortic root dilatation.

### SURGERY

The operative and hospital mortality rate in patients with dissection from all causes was 29%, and late mortality was 5% (Table 4). The hospital mortality rate in patients with aortic dilatation without dissection was 8%; in those with ascending and transverse aortic dilatation it was 9%, and late mortality was also 9% in this group (Table 5).

Among patients with acute dissection, there were 10 (41%) operative and hospital deaths and one late death. Among patients with dissection who had elective surgery there were two (12%) hospital deaths (one (8%) in 12 cases of chronic ascending aortic dissection) and one late death at reoperation three months after the first operation. Among the three cases of rupture of the transverse aorta there were no hospital or late deaths.

There were six (31%) deaths among 19 patients with severe aortic regurgitation and aneurysms (8) or dissection (11) who were given a composite graft with a valve prosthesis and had reimplantation of the coronary arteries.

One of the three patients with aneurysms of the ascending aorta and severe aortic regurgitation (in whom a valve prosthesis and a vascular prosthesis were implanted) died in hospital (case 48). In patients with Marfan's syndrome and type I dissection there were no hospital deaths and one late death (Table 4). All seven patients with aortic dilatation without dissection survived (Table 5). In subjects with hypertension, there were six (31%) operative or hospital deaths, three in patients with type I dissections, one in a patient with type II dissection, and two in patients with type III dissection (Table 4). One hypertensive patient with dilatation of the ascending aorta without dissection died in

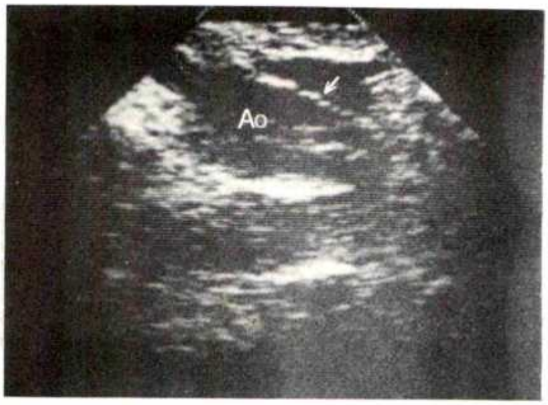

Fig. 3 *An echocardiogram in case 57 suggesting the presence of dissection of transverse aorta. Dissection was excluded at angiography and at surgery. Arrow indicates the line responsible for the misinterpretation. Ao, aorta.*

Table 4 *Surgical results in cases of acute and chronic dissections according to cause*

| | No of patients | Operative deaths | Hospital deaths | Late deaths |
|---|---|---|---|---|
| *Acute aortic dissection:* | 24 | 5 | 5 | 1 |
| Connective tissue disease | 5 | | | |
| Hypertension | 10 | 2 | 3 | |
| Other cause | 2 | 1 | | 1 (at 4 months) |
| Unknown cause | 7 | 2 | 2 | |
| *Chronic aortic dissection:* | 17 | 1 | 1 | 1 |
| Connective tissue disease | 3 | | | 1 (at 3 months)* |
| Hypertension | 9 | | 1 | |
| Other cause | 2 | 1 | | |
| Unknown cause | 3 | | | |
| *Type I dissection (acute and chronic):* | 24 | 5 | 3 | 2 |
| Connective tissue disease | 8 | | | 1 |
| Hypertension | 8 | 2 | 1 | |
| Other cause | 2 | 1 | | 1 |
| Unknown cause | 6 | 2 | 2 | |
| *Type II dissection (acute and chronic):* | 10 | 1 | 1 | |
| Connective tissue disease | | | | |
| Hypertension | 5 | | 1 | |
| Other cause | 2 | 1 | | |
| Unknown cause | 3 | | | |
| *Type III dissection (acute and chronic):* | 7 | | 2 | |
| Connective tissue disease | | | | |
| Hypertension | 6 | | 2 | |
| Other cause | | | | |
| Unknown cause | 1 | | | |

*This patient required reoperation.

hospital. There were no late deaths in patients with hyertension (Table 5).

Among patients with aneurysms with other causes and with dissection of the ascending aorta there were two operative deaths and one late death (Table 4). In patients in this group with dilatation and without dissection there was one late death (Table 5). In the group with aneurysms of unknown cause there were four (40%) hospital deaths, all in patients with type I dissection (Table 4); in the six cases with dilatation without dissection there was one hospital death and one late death (Table 5).

### FOLLOW UP AND CAUSE OF DEATH

In the patients with aortic dissections the causes of hospital deaths were bleeding in six, septicaemia with renal failure in three, mediastinitis in one, and cerebral ischaemia with progressive stage IV coma due to recurrent dissection of the aortic arch in one. Bleeding and septicaemia caused two late deaths. In patients with aortic dilatation only, hospital deaths were the result of mediastinitis in one and low cardiac output in the other. There were two late deaths, one in a patient who died suddenly, presumably from arrhythmia, and the other from bleeding.

Table 5 *Surgical results in cases of dilatation without dissection according to cause*

| | No of patients | Operative deaths | Hospital deaths | Late deaths |
|---|---|---|---|---|
| *Aneurysms of ascending aorta:* | 15 | — | 2 | 1 |
| Connective tissue disease | 6 | — | — | — |
| Hypertension | 4 | — | 1 | — |
| Other cause | 2 | — | — | — |
| Unknown cause | 3 | — | 1 | 1 (at 3 months) |
| *Aneurysms of transverse aorta:* | 7 | — | — | 1 |
| Connective tissue disease | 1 | — | — | — |
| Hypertension | 1 | — | — | — |
| Other cause | 2 | — | — | 1 (at 10 months) |
| Unknown cause | 3 | — | — | — |
| *Aneurysms of descending aorta.* | 2 | — | — | — |
| Connective tissue disease | — | — | — | — |
| Hypertension | 2 | — | — | — |
| Other cause | — | — | — | — |
| Unknown cause | — | — | — | — |

Table 6 *Postoperative angiography and contrast enhanced computed tomography results in 24 of 35 survivors at operation for dissection*

| *Dissection* | *No of patients* | *Angiography* | | *Contrast enhanced computed tomography* | |
|---|---|---|---|---|---|
| | | *Normal* | *Distal dissection* | *Normal* | *Distal dissection* |
| Type I | 19 | | 8 | 4 | 7 |
| Type II | 9 | 1 | 1 | 2 | 1 |
| Type III | 7 | | 3 | 2 | |

Both angiography and contrast enhanced computed tomography were performed in five patients, four of whom had type I dissection.

In patients undergoing postoperative angiography and contrast enhanced computed tomography or both (Table 6) distal dissections were common (16/24, 66%). In the five patients in whom both angiography and contrast enhanced computed tomography were performed the diagnoses by the two methods were the same (four had type I and one had type II dissections).

Reoperation was necessary in three patients, two for bleeding and one for abdominal ischaemia resulting from compression of the true lumen by the false one. One patient with Marfan's syndrome and type I dissection (case 27) who had reoperation for bleeding and distal dissection after three months died of persistent bleeding and cardiac tamponade; the patient with hypertension and type I dissection (case 38) who had reoperation for abdominal ischaemia one year later is alive and symptom free; the patient with a formes fruste of Marfan's syndrome and dilatation of the transverse aorta (case 44) who had reoperation for bleeding two days later is also alive and symptom free.

No case of paraplegia—which is a frequent complication of operating on descending thoracic aortic aneurysms—was observed in the present series. This absence of neurological sequelae underscores the safety and usefulness of the femoral vein-femoral artery bypass in treating descending thoracic aneurysms.

## Discussion

### CAUSE AND TYPE OF AORTIC LESION

In this series men outnumbered women whatever the cause of the aneurysms; patients with acute aortic dissections were younger than those with chronic aortic dissection, and patients with Marfan's syndrome and type I dissections were younger than patients with hypertension and type III dissections. Eight patients with type I dissections, seven with dilatation only, and one with rupture of an undilated transverse aorta, were deemed to have connective tissue disease. It is likely that the number of such patients would have been greater if more skeletal and ophthalmological examinations had been performed or if less restrictive criteria had been followed. No patient with Marfan's syndrome had type III dissection or dilatation of only the descending aorta. All eight patients with type III dissection (six cases) and dilatation of the descending aorta (two cases) had hypertension.

### HISTOLOGICAL EXAMINATION

We expected that histological examination would be helpful in reaching a diagnosis in patients with aneurysms of unknown cause. In fact, it was of no help. On the basis of our results, and according to those reported by others (*a*) cystic medial necrosis (pooling of mucoid material); (*b*) elastin fragmentation (disruption of elastin lamellae); (*c*) fibrosis (increase in collagen at the expense of smooth muscle cells); and (*d*) medionecrosis (areas with apparent loss of nuclei) increase progressively with age independently of the presence of arterial hypertension.[8 9]

The variability of the degree of cystic medial necrosis in Marfan's syndrome accords with reports of minimal histological lesions in patients with Marfan's syndrome and aortic dissection.[10] Thus diagnosis of Marfan's syndrome can only be based on a thorough clinical examination to detect skeletal, ocular, and cardiac manifestations.

### SURGERY

The mortality rate in the whole series was 26%. Early (operative and hospital) and late deaths occurred in 20% and in 6% of patients respectively. Early deaths occurred in 40% of acute cases of ascending aortic dissection, in 9% of patients operated on for dilatation of ascending and transverse aorta without dissection, and in 8% of patients with chronic dissection of the ascending aorta who had elective surgery.

Our results with surgery of acute ascending aortic dissection in 15 of 22 patients in whom medical treatment was contraindicated compare favourably with the mortality rate in untreated patients.[11 12] There was one early postoperative death among seven patients with dissection of the ascending aorta in whom medical treatment had produced stabilisation of the clinical state. Our operative mortality in these cases compares favourably with the mortality rate in patients treated medically.[11–13]

Table 7 *Contrast enhanced computed tomography (CT) and angiography in 10 patients with echocardiographic diagnosis of dilatation of the ascending aorta*

| *Case No* | *Echocardiography** | *CT scan** | *Angiography* |
|---|---|---|---|
| 27 | Dilatation | Dissection | Type I dissection, SAR |
| 30 | Dilatation | Dissection | Type I dissection, SAR |
| 50 | Dilatation (80 mm) | Dilatation (88 mm) | AAA, SAR |
| 52 | Dilatation (68 mm) | Dilatation (70 mm) | AAA, SAR |
| 53 | Dilatation (57 mm) | Dilatation (62 mm) | AAA, SAR |
| 54 | Dilatation (51 mm) | Dilatation (53 mm) | AAA, SAR |
| 55 | Dilatation (60 mm) | Dilatation (64 mm) | AAA, SAR |
| 56 | Dilatation (50 mm) | Dilatation (55 mm) | AAA, SAR |
| 60 | Dilatation (58 mm) | Dilatation (62 mm) | AAA |
| 64 | Dilatation (67 mm) | Dilatation (74 mm) | AAA |

*Numbers in parentheses are aortic root diameter measurements.
Dilatation, aortic root dilatation; dissection, aortic root dissection; AAA, ascending aortic aneurysm; SAR, severe aortic regurgitation.

The chronic dissections of the ascending aorta of our series were asymptomatic (60%) or at a relatively stable stage (onset of symptoms 20 days or longer before diagnosis and medical treatment). Our early and late postoperative mortality rate was lower than that in medically treated patients.[14]

Dissections of the descending aorta in our series were associated with a mortality rate of 29%. This rate is below that observed by Dalen *et al*[15] and similar to that reported by Miller *et al*[16] in medically treated patients. In the 22 patients with dilatation of the ascending and transverse aorta there were two early and two late deaths. The early and late mortality rates in this group of patients are lower than that in untreated patients.[17 18]

The mortality rate in patients with connective tissue disease who were operated on for dissection or dilatation of the ascending aorta was no higher than the rate in other causal groups; these results are not affected by the inclusion in the group with connective tissue disease of patients aged <40 years in whom the aetiology of aneurysms was described as "unknown" or "other". Thus the risks of operation in patients with Marfan's syndrome do not seem to be increased and their postoperative prognosis in the midterm does not appear to be particularly poor. The implication of this clinical observation is limited by the fairly small numbers of patients we studied.

### ECHOCARDIOGRAPHY AND CONTRAST ENHANCED COMPUTED TOMOGRAPHY

Echocardiography is the most commonly used non-invasive test for detecting aneurysms of the ascending aorta and serial echocardiographic evaluation is the most practicable method of following up these lesions. Accurate estimation of aortic root dilatation by M mode echocardiography, however, is difficult.[19] Dilatation is often more evident and more pronounced several centimetres above the valve plane.[20] The lack of correlation between aortic root dilatation and echocardiographic or auscultatory signs of aortic regurgitation may be explained by the difficulty of defining where dilatation starts, especially when it is eccentric, and whether the aortic valve is affected.[21] Cross sectional echocardiography is better than M mode echocardiography for the non-invasive location of aneurysms of the ascending aorta and for determining their extent. The addition of contrast enhanced computed tomography to the diagnostic procedure improved the accuracy of investigation of these lesions in some cases. Preoperative serial echocardiography was not performed in follow up of cases with chronic aortic dissection because dissection requires immediate operation even in symptom free patients. Serial echocardiography had been performed before operation in a follow up of 13 patients in whom aortic root dilatation without dissection had been diagnosed and ten of these also had contrast enhanced computed tomography (Table 7). Contrast enhanced computed tomography was required to confirm the echocardiographic diagnosis when the increased aortic root measurement indicated important progression of disease and in all patients with pronounced aortic root dilatation. In two patients with severe aortic root dilatation (cases 27 and 30) dissection of the ascending aorta was recognised (Fig. 1). In the others echocardiographic diagnoses were confirmed and dissections excluded (Fig. 2). The same diagnoses were reached by contrast enhanced computed tomography and angiography.

In our series cross sectional echocardiography did not detect aortic root dissection in four (21%) out of 19 patients. Because chronic dissection may be missed by echocardiography, we propose that contrast enhanced computed tomography should be performed in patients with aneurysms in whom echocardiography has not been technically satisfactory, in all patients with pronounced aortic root dilatation or an important increase in dilatation, and in patients with connective tissue disease and symptoms that suggest dissection in the absence of supporting evidence, even those who have only minimal aortic root dilatation. Dissection has been reported in patients with Marfan's syndrome without dilatation of the aortic root.[10]

Postoperatively contrast enhanced computed tomography was used as an outpatient test for evaluating surgical results and for following up distal postoperative dissections. The results of contrast enhanced computed tomography indicated that reoperation should be performed in one case (case 38).

Non-invasive assessment techniques may be of value in identifying patients in whom preventive replacement of the ascending aorta might avoid emergency operation which increases surgical mortality. Donaldson *et al* believe that preventive replacement of the ascending aorta is indicated in symptom free patients with Marfan's syndrome and a large (diameter determined by M mode echocardiography $>60$ mm) progressively dilating aortic root or dilated left ventricle (end systolic dimension greater than 55 mm in cases of aortic regurgitation).[22] McDonald *et al* believe that preventive replacement of the ascending aorta should be performed when the aortic root diameter determined by M mode echocardiography is $>55$ mm.[23] When the aortic root is 55–60 mm in diameter and the plane of the aortic valve is affected, however, there is almost always severe aortic valve regurgitation which in itself requires replacement of the ascending aorta. Furthermore, there may be severe aortic valve regurgitation when echocardiographic measurement indicates an aortic root diameter of $<55$ mm (Table 7). Symptom free patients in whom the aortic root is dilated to $>55$ mm without affecting the aortic valve plane and without progressive dilatation of the aortic root do not require preventive replacement of the ascending aorta. In some patients it is difficult to demonstrate a progressive slow dilatation of the aorta by echocardiography alone. When the aortic root is less than 55 mm in diameter but echocardiography and contrast enhanced computed tomography or both have demonstrated a recent rapid progression of dilatation, especially when the aortic valve is affected, prophylactic replacement of the ascending aorta should be considered.

There seems to be no defined limit to aortic root dilatation above which replacement of the ascending aorta should be routinely considered. Even in symptom free patients severe aortic valve regurgitation, the presence of dissection, and the demonstration of rapid dilatation of the aortic root are indications for replacement of the ascending aorta.

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# Negative right ventricular diastolic pressure after operation for pulmonary valve stenosis: the phenomenon and its relation to volume load and conal contraction

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SUMMARY The phenomenon of negative right ventricular diastolic pressure immediately after operation for relief of isolated pulmonary valve stenosis was investigated in 11 patients. Pressures in the right ventricle and pulmonary artery were measured with a catheter tip micromanometer. One patient had a negative right ventricular diastolic pressure before operation. At the end of operation right ventricular diastolic pressure was negative in all 11 patients. The greater the right ventricular hypertrophy, the lower were these diastolic pressures. Negative right ventricular diastolic pressure is thus common in patients after pulmonary valvotomy, but fluid administration may eliminate it. Negative right ventricular diastolic pressure may be the result of hypercontraction and reduced volume of the hypertrophied right ventricle after relief of right ventricular outflow tract obstruction.

Negative diastolic pressure mostly in the left ventricle has been demonstrated in animal and in human experiments,[1–5] as well as in conditions such as mitral stenosis[5 6] or after rapid exsanguination.[7 8]

Sabbah and Stein among others showed that negative diastolic pressures can also be demonstrated in the right ventricle.[9 10] Diastolic pressure in the right ventricle of a patient with pulmonary stenosis may be normal or raised when severe obstruction or right ventricular failure is present.[11] Our incidental observation that negative right ventricular diastolic pressure was common after pulmonary valvotomy[12] prompted us to more detailed study of right ventricular pressure after pulmonary valve operation.

## Patients and methods

Eleven patients (aged 2–58, median 14·7 years) undergoing elective operation for isolated pulmonary valve stenosis were studied prospectively. Table 1 shows their preoperative clinical characteristics and right ventricular catheterisation data. Preoperative symptoms included cyanosis in three, finger clubbing in three, effort dyspnoea in three, and congestive heart failure in two. Three of the patients were symptom free. Right ventricular hypertrophy was noted in 10 patients.

Mean right ventricular systolic pressure was 107·5 (52·5) mm Hg (range 46–240). Preoperative right ventricular diastolic pressure ranged from −2 to 25 mm Hg (mean 11·36 (8·5) mm Hg). Only one patient had negative diastolic pressure before operation. Three of the patients had appreciable conal contraction on preoperative angiograms, but all three showed relaxation of the right ventricular outflow tract during diastole. All operations were performed by means of an open heart technique. Dome shaped valves were treated by sharp commissurotomy up to the valve ring. Four patients who had dysplastic valves underwent partial or complete excision of the valve (valvectomy). A transannular patch was used in a patient with a dysplastic valve and small pulmonary annulus. Infundibular

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Accepted for publication 21 August 1985

resection was used in one patient with infundibular muscular hypertrophy and important obstruction of the right ventricular outflow tract. In three patients who had either associated atrial septal defect or patent foramen ovale had it closed. We measured pressures in the right ventricle and pulmonary artery with a catheter tip micromanometer (Millar Instruments) immediately after discontinuation of cardiopulmonary bypass. The frequency response of the pressure sensor was almost flat (±2%) at 5 kHz. The zero baseline of the transducers was adjusted to atmospheric pressure before each set of measurements. Recordings were obtained on Electronics for Medicine VR-6. The frequency response of the recording system was flat to 700 Hz.

Diastolic pressures were measured twice in the right ventricle; firstly after the end of cardiopulmonary bypass. At this stage the heart did not appear to be distended or collapsed and the level of the blood in the oxygenator was about the same as before onset of cardiopulmonary bypass (central venous pressure (4–7 mm Hg). The second measurement was taken while the chest was still open, approximately 10 to 15 minutes later, after the patient's condition had stabilised and after an additional volume of blood (mean 10 ml/kg pump blood) had been administered. Preoperative and postoperative right ventricular pressures were compared by the paired Student's *t* test.

## Results

In all eleven patients postoperative right ventricular diastolic pressure was negative (−14 (7·2)) mm Hg and significantly lower than the preoperative pressure ($p<0\cdot001$) (Table 2, Fig. 1). Pressures as low as −28 mm Hg were noted (Fig. 2). The negative diastolic pressures were measured in the body and in the infundibulum of the right ventricle. Pulmonary artery diastolic pressure was negative in three patients after pulmonary valvectomy (cases 1, 3, 4) and in one after infundibular resection and transannular patching (case 7). The pressure in the right ventricle was negative during most of diastole. In all patients right ventricular diastolic pressure was lowest during the early phase of rapid ventricular filling (Fig. 3).

Volume load tended to reduce or eliminate the negative pressure (Fig. 4, Table 2). Negative diastolic pressures below −10 mm Hg were observed only in patients with preoperative right ventricular : left ventricular systolic pressure ratios higher than 0·9 (Fig. 5).

The subgroup of patients with low right ventricular : left ventricular ratios (<0·9) had significantly higher postoperative diastolic right ventricular pressures compared with the subgroup in which the ratio was high (−6·75 (2·9) *vs* −18·2 (6) mm Hg) ($p<0\cdot001$).

Table 1 *Characteristics of 11 patients before pulmonary valve operation*

| *Case No* | *Age* | *Sex* | *Symptoms* | *RVH* | *Sys BP (mm Hg)* | *RV sys (mm Hg)* | *RV dias (mm Hg)* | *RV/LV* | *Subvalvar obstruc* | *Associated PFO* | *Dysplastic valve* | *Operation* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 4 | M | Tiredness | + | 100 | 130 | 12 | 1 3 | − | − | + | Valvectomy* and transannular patch |
| 2 | 5 | F | Cyanosis, clubbing | + | 100 | 98 | 0 | 0 98 | − | − (?) | + | Valvectomy |
| 3 | 4 5 | F | Cyanosis, clubbing | ++ | 115 | 104 | 25 | −0 9 | − | + | + | Valvectomy |
| 4 | 58 | F | CHF, dyspnoea | ++ | 120 | 120 | 10 | 1 | + | − | + | Valvectomy |
| 5 | 2 | F | — | + | 102 | 88 | 22 | 0 86 | − | − | − | Valvotomy |
| 6 | 6 5 | M | CHF, | + | 100 | 100 | 20 | 1 | − | − | − | Valvotomy |
| 7 | 15 | F | effort dyspnoea | ++ | 120 | 240 | 20 | 2 | ++ | − | − | Valvotomy and infundibular resection |
| 8 | 6 | M | Cyanosis | (−) | 118 | 46 | −2 to +4 | 0·39 | − | + | − | Valvotomy and incomplete closure of PFO |
| 9 | 6 | M | — | + | 110 | 62 | 0 | 0 56 | − | − | − | Valvotomy and closure of ASD |
| 10 | 48 | M | Dyspnoea, palpitation | + | 126 | 134 | 2 | 1 06 | + | + | − | Valvotomy and closure of ASD |
| 11 | 7 5 | F | Dyspnoea | + | 105 | 60 | 16 | 0 57 | − | − | − | Valvotomy |
| Mean | 14 7 | | | | | 107·5 | 11·36 | 0 96 | | | | |
| (SD) | (16) | | | | | (52 5) | (8 5) | (0 43) | | | | |

*Valvectomies were performed only in patients with dysplastic pulmonary valves.
CHF, congestive heart failure; RVH, right ventricular hypertrophy on electrocardiogram, Sys BP, systemic blood pressure (systolic); RV sys, systolic right ventricular pressure, RV dias, diastolic right-ventricular pressure; PFO, patent foramen ovale.

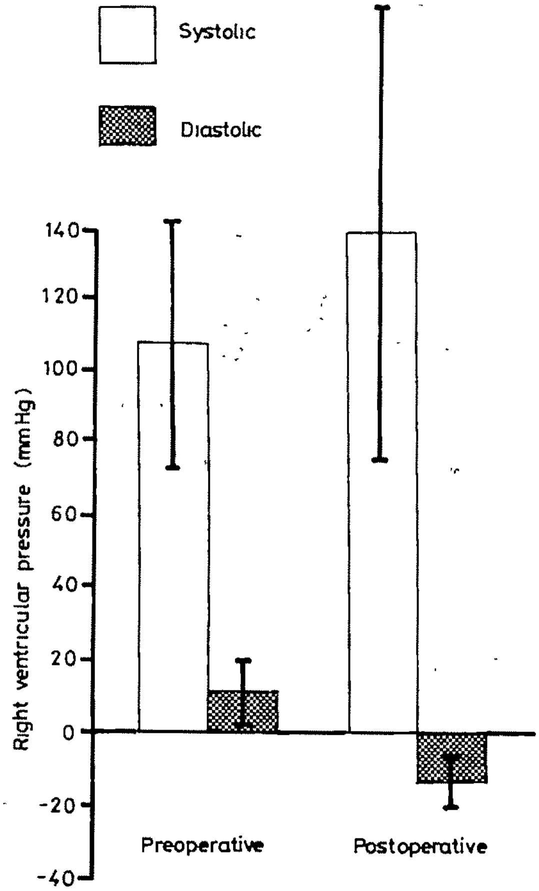

Fig. 1 · *Effect of pulmonary valve operation on right-ventricular pressure.*

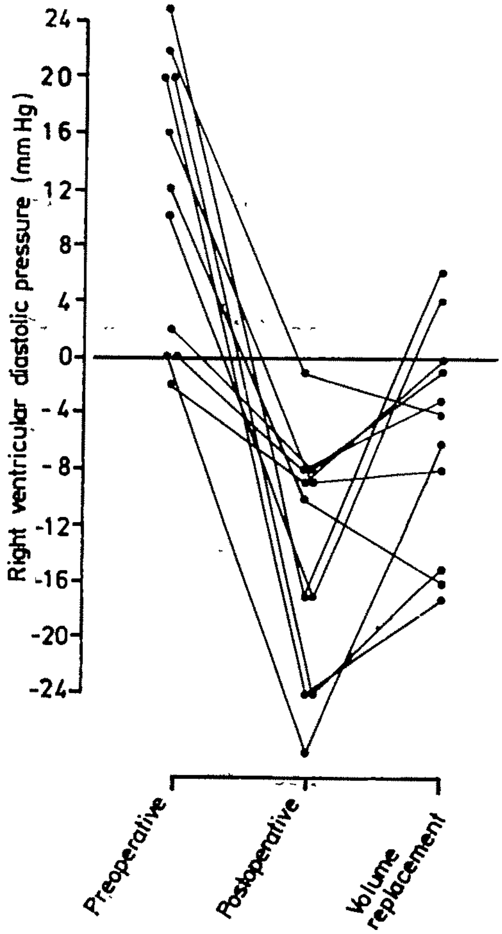

Fig. 2 *Effect of pulmonary valve operation on minimum diastolic pressure in the right ventricle. Minimal diastolic pressure after administration of blood for volume replacement is also shown.*

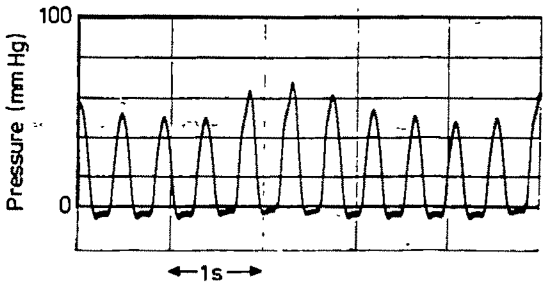

Fig. 3 *Right ventricular pressure tracing after pulmonary valvotomy.*

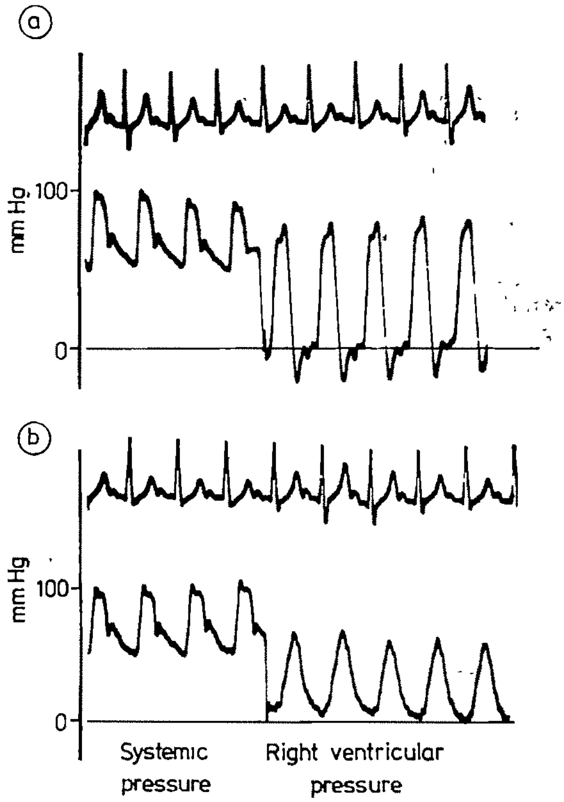

Fig. 4 *Increase of right ventricular diastolic pressure after volume replacement in a patient after pulmonary valvotomy. (a) After valvotomy and (b) after volume replacement.*

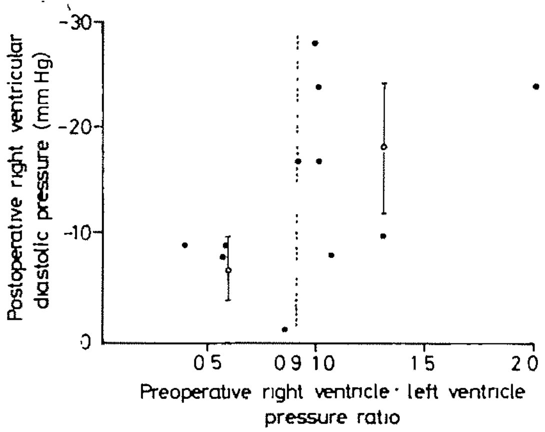

Fig. 5 *Relation between preoperative right ventricle: left ventricle pressure ratio and postoperative right ventricular diastolic pressure.*

Table 2 *Right ventricular and pulmonary artery pressures at end of cardiopulmonary bypass in 11 patients after pulmonary valvotomy*

| *Case No* | *BP (mm Hg)* | | *RV initial (mm Hg)* | | *Infundibulum (mm Hg)* | | *Pulmonary artery (mm Hg)* | | *RV after volume load (mm Hg)* | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *Sys* | *Dias* | *Sys* | *Dias* | *Sys* | *Dias* | *Sys* | *Dias* | *Sys* | *Dias* |
| 1 | 120 | 80 | 120 | −10 | 119 | −10 | 15 | −5 | 118 | −16 |
| 2 | 110 | 80 | 116 | −28 | | | | | 100 | −6 |
| 3 | 130 | 80 | 200 | −17 | 200 | −17 | 30 | −14 | 130 | |
| 4 | 110 | 80 | 214 | −17 | 128 | −12 | 18 | −6 | 135 | 4 |
| 5 | 105 | 57 | 207 | −1 | 200 | −1 | | | 113 | −4 |
| 6 | 110 | 70 | 105 | −24 | | | | | 117 | −15 |
| 7 | 130 | 80 | 285 | −24 | 195 | −18 | 40 | −12 | 170 | −17 |
| 8 | 101 | 70 | 35 | −9 | | | 14 | 3 | 48 | 0 |
| 9 | 120 | 80 | 111 | −8 | 110 | −8 | 12 | 4 | 100 | −1 |
| 10 | 107 | 90 | 109 | −8 | 75 | −6 | 23 | 7 | 88 | −3 |
| 11 | 121 | 67 | 31 | −9 | | | | | 38 | −8 |
| Mean (SD) | 115 (9 8) | | 139 3 (78 4) | −14 (8·5) | | | | | 105 1 (37·7) | −6 6 (7 2) |

BP, systemic blood pressure; RV, right ventricular pressure; dias, diastolic, sys, systolic.

## Discussion

Postoperative right ventricular diastolic pressure was negative in all 11 patients operated upon. In nine of the eleven cases volume loading reduced the degree of the negative pressure in the right ventricle. This may indicate some degree of hypovolaemia in these patients. Indeed, exsanguination and hypovolaemia have been reported in association with the development of negative ventricular pressure.[6 8-]

Hypercontraction of the hypertrophied right ventricle after relief of long standing overload may be the main factor producing negative pressure in the present series. This is supported by the lower right ventricular diastolic pressure in patients with the greater preoperative right ventricular hypertrophy (right ventricular: left ventricular ratios >0·9) (Fig. 5).

It has been shown that reduced end systolic volume is associated with negative diastolic ventricular pressures.[2 3] It is also recognised that once pulmonary stenosis is relieved the contraction of the right ventricular conus is more complete,[13] and this may result in further contraction of end systolic right ventricular volumes. Whether the main factor in producing negative ventricular diastolic pressure is hypovolaemia or hypercontractility, end systolic volume always seems to be reduced.[1-8]

We found negative diastolic pressures in the pulmonary artery after valvectomy or valvectomy with transannular patching. By causing pulmonary valve insufficiency these procedures may have a deleterious effect on the right ventricle.[14]

It has been suggested that negative diastolic pressures may be associated with a suction effect.[2 3 15] Under such circumstances, the ventricles contract to a volume smaller than that of their "elastic equilibrium volume" and smaller than that achieved at rebound by "elastic recoil", and thus cause the negative pressure and its suction effect.[2 3 15] Deformation of some components of the ventricle during systole may produce the potential energy for an elastic recoil during diastole.[1 15]

It is clear that negative right ventricular diastolic pressure is common immediately after isolated pulmonary valvotomy and should be taken into account during volume loading at the end of cardiopulmonary bypass.

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*Br Heart J* 1986; 55: 97–100

# Profound bradycardia after amyl nitrite in patients with a tendency to vasovagal episodes

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SUMMARY Two patients with mild aortic insufficiency inhaled amyl nitrite during routine echocardiographic examinations. One developed sinus arrest and syncope and the other had pronounced sinus bradycardia. The mechanism of this paradoxical response is unclear. Caution should be exercised when amyl nitrite is administered for diagnostic purposes.

Amyl nitrite is routinely used during physical and echocardiographic examinations for the evaluation of cardiac murmurs. This vasoactive agent generally causes dilatation of peripheral arteries and veins and striking tachycardia. We report an atypical and potentially dangerous response to amyl nitrite in two patients.

## Case reports

### PATIENT 1

A 32 year old man was referred for echocardiography for evaluation of a murmur after he had fainted when a phlebotomy needle was inserted. On another occasion, he had noted pronounced lightheadedness after blood donation. He denied other symptoms of cardiac disease. Physical examination revealed a short murmur of aortic regurgitation.

A baseline M mode echocardiogram performed with the patient supine was normal. Resting heart rate was 58 beats per minute. Seconds after inhaling amyl nitrite, and while he was still supine, the patient complained of lightheadedness. The technician noted that the patient was sweating profusely, and shortly afterwards he became unresponsive. Figure (a) is the M mode echocardiogram at the level of the mitral valve obtained immediately before and immediately after onset of the syncopal episode. After amyl nitrite inhalation the patient's heart rate initially slowed to 40 beats per minute. All atrial and ventricular electrical activity disappeared, and recorded cardiac motion ceased for 10 s. The technician attempted to arouse the patient, who became responsive after 3–5 s. Resumption of the echocardiographic record showed three junctional beats, followed by sinus rhythm at 60 beats per minute. When he was examined shortly after the episode the patient was peripherally constricted and sweating and complained of mild dizziness. The pulse rate was 56 beats per minute, blood pressure 110/70 mm Hg, and the respiratory rate was 18 per minute. Cardiovascular and neurological examinations were unremarkable and repeat M mode and cross sectional echocardiograms were normal. The results of carotid sinus massage, hyperventilation, biochemical analysis of blood, 24 hour ambulatory electrocardiographic monitoring, and exercise stress test did not disclose any abnormality. The patient was told to avoid venepuncture. He remains symptom free.

### PATIENT 2

A 32 year old man was referred for evaluation of a murmur that had been detected one month earlier at routine physical examination. He complained of severe anxiety leading to nausea, lightheadedness, sweating, and syncope. He recalled at least eight previous syncopal events, all associated with either medical visits or venepuncture. He had no other cardiac symptoms. Physical examination was normal apart from a I/IV early diastolic decrescendo blowing murmur at the base of the heart. Electrocardiogram and chest radiography were normal. M mode echocardiographic examination showed fine diastolic fluttering of the anterior mitral leaflet with normal chamber dimensions. After inhalation of amyl nitrite the sinus rate fell progressively from 78

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Accepted for publication 5 August 1985

to 30 beats per minute (Fig. (b)) and the patient complained of lightheadedness. The pulse rate then increased gradually.

Electrocardiographic examination during carotid sinus massage and hyperventilation, cross sectional echocardiography, 24 hour ambulatory electrocardiographic monitoring, and exercise stress test showed no abnormalities.

## Discussion

These two apparently healthy patients had paradoxical bradycardia after inhalation of amyl nitrite. One had sinus arrest with loss of consciousness while supine. Although both had short murmurs characteristic of aortic insufficiency, neither had evidence of haemodynamically important cardiovascular disease. They were taking no medications. To our knowledge, sinus bradycardia and arrest after amyl nitrite inhalation have not been described before. Inhaled amyl nitrite enters the circulation rapidly, producing sudden and pronounced arteriolar and venous dilatation. The fall in systemic blood pressure results in reflex stimulation of the sympathetic nervous system, producing sinus tachycardia and pronounced venoconstriction, both of which contribute to the increase in cardiac output. Reflex arteriolar constriction occurs as well.[1 2] Amyl nitrite induces more pronounced reflex vasoconstriction than glyceryl trinitrate.

In patients with severe coronary stenosis, cardiac output may fall after nitrate administration if the induced hypotension intensifies ischaemia.[3] Come and Pitt described syncope in five patients with myocardial infarction.[4] They developed hypotension and bradycardia without preceding tachcardia after they had been given sublingual or intravenous glyceryl trinitrate in the first 24 hours after myocardial infarction.

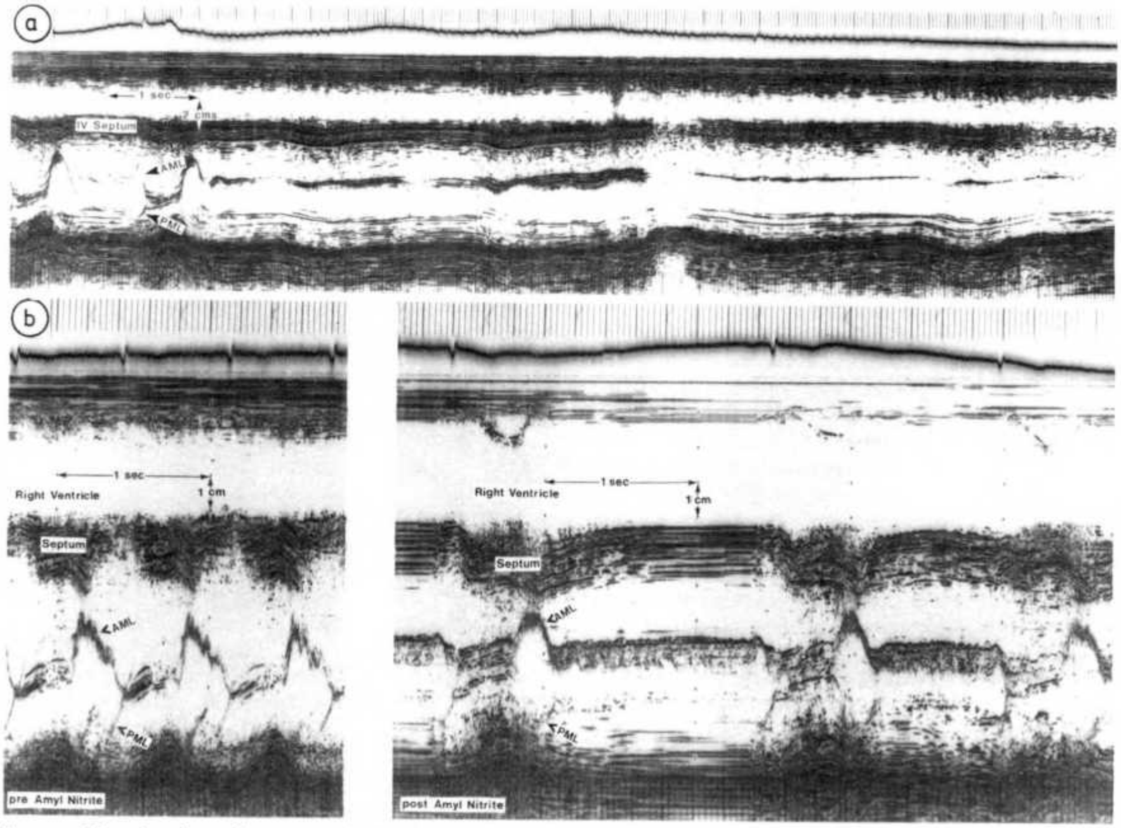

Figure *M mode echocardiograms at the level of the mitral valve several seconds after amyl nitrite inhalation. (a) In patient 1 two sinus beats were followed by prolonged asystole. (b) In patient 2 the sinus rate slowed to 30 beats per minute. There is evidence of diastolic fluttering of the mitral valve. AML, anterior mitral leaflet; PML, posterior mitral leaflet; IV septum, interventricular septum.*

Nitrate induced syncope is not restricted to patients with coronary artery disease.[5 6] Studies of normal volunteers on tilt tables have suggested that decreased effective circulating blood volume secondary to dependent venous pooling may cause circulatory collapse,[7 8] and that this reaction may be intensified by the administration of sodium nitrite.[9 10] Such reactions are characterised by constant central venous pressure, gradually falling arterial pressure, and complaints of sweating, nausea, abdominal cramps, and dizziness. Abrupt falls in blood pressure and heart rate may follow. Loss of consciousness may be prevented by returning the subjects to the supine position, negative pressure breathing, or albumin infusion. Atropine prevents bradycardia but not syncope. These haemodynamic responses have been ascribed to parasympathetic reflexes induced by ischaemia of the medulla oblongata[10] or by left ventricular cavitary obliteration.[8] The theory that cerebral ischaemia causes the bradycardia has been questioned because changes in heart rate precede electroencephalographic changes. In the two patients described here, there was no obliteration on the M mode echocardiograms at the time the haemodynamic changes occurred.

Vagal reflexes are often implicated in syncope associated with bradycardia. Because reflex asystole rarely lasts more than 10 s, and 15 s of asystole are generally required to produce unconsciousness in the recumbent position, reflex mediated syncope is unusual in a supine patient.[11] There are multiple afferent pathways which may lead to vagally induced bradycardia, asystole, and vasodilatation. Afferent fibres originate in the heart, arterial vessels, respiratory and gastrointestinal tracts, the ear, and the trigeminal and glossopharyngeal nerves. Hypersensitivity is extremely variable, and is subject to influences such as hypoxia and medications.[12] There are many intracardiac reflexes.[13] The coronary chemoreflex, also mediated by the vagus nerve, produces a fall in blood pressure and heart rate after intracoronary injection of chemicals such as digitalis, nicotine, adenosine triphosphate, serotonin, phenyl diguanide, and isothiourea.[14 15] The effects of amyl nitrite on this reflex have not been examined. Cardiac pressor reflexes after an increase of intracavitary pressures result in bradycardia and hypotension.[16 17] Intense vasodilatation and bradycardia, as well as decreased venous return, have been induced in dogs by acute increases in left ventricular pressure.[18-20] Appreciable increases in left ventricular pressure after amyl nitrite administration, however, have not been demonstrated.

Glossopharyngeal neuralgia may cause bradycardia and syncope,[21] and similar bradycardias have been described in patients with "swallow syncope" in association with oesophageal lesions.[22 23] Our patients had no history of mandibular pain or symptoms referable to the oesophagus. Several inhaled gases, such as ammonia, phosgene, and bromine vapour, cause vagally mediated reductions in heart rate and blood pressure. These may act on chemoreceptors in the lung or may be systemically absorbed and act at other sites.[12] Amyl nitrite, despite its broad clinical use, has not been associated with pulmonary chemoreflexes.

Because these patients were told to inhale deeply when amyl nitrite was administered, some degree of hyperventilation induced hypocapnia may have resulted. Hypocapnia intensifies cerebral vasoconstriction,[24] and, therefore, may contribute to centrally mediated syncope. Neither patient, however, developed symptoms of hypocapnia, nor did hyperventilation at a later time reproduce the bradycardia or syncope.

The cause of the bradycardia in these patients is unclear. Neither of the patients responded to amyl nitrite with early tachycardia. In patient 1, a trained athlete, relative insensitivity of cardiac beta receptors may have contributed to lack of a chronotropic response,[25] but patient 2 had a sedentary lifestyle. In both, bradycardia was the first manifestation of this unusual reaction.

It is important to note that bradycardia and sinus arrest may occur as an unexpected reaction to amyl nitrite inhalation. Administration of this agent has been considered to be a routine procedure without known serious sequelae. Although the complication noted in this report is probably rare, we feel that the use of amyl nitrite should be avoided in patients with unexplained syncope. This agent should be administered by staff who are trained in cardiopulmonary resuscitation and atropine and appropriate resuscitative equipment should be available.

We thank Dr Dennison Young for permission to describe his patient.

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# Cardiac valve prostheses, anticoagulation, and pregnancy

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SUMMARY The course of 76 pregnancies is reported in 51 women who became pregnant after replacement of one or more heart valves. Age at conception ranged from 17 to 39 years (mean 25). There have been 71 deliveries and five women are still pregnant at the time of writing. In the 71 pregnancies, oral anticoagulants were given during 53, heparin during five, and no anticoagulants during 13. Fetal complications consisted of 12 spontaneous abortions (eight in pregnancies in which oral anticoagulants were given, three in which heparin was given, and one in which no anticoagulants were given), of 12 premature deliveries with seven stillbirths (three on oral anticoagulants and four without anticoagulants), and there were three neonatal deaths (in all three instances oral anticoagulants had been given during pregnancy). The maternal complications were as follows. Two women with mitral valve prostheses on heparin had thromboembolic episodes. Four women on oral anticoagulants died and 11 developed haemorrhage or systemic embolism. Two of the deaths were caused by bacterial endocarditis, one was the result of obstruction of a mitral valve prosthesis, and one was due to haemorrhage. One patient developed pulmonary oedema during delivery which rapidly resolved. Seven patients had uterine bleeding after delivery (three of them were on heparin and one was on an antiplatelet agent).

In 1966 DiSaia reported the first pregnancy and delivery in a patient with a Starr-Edwards valve prosthesis.[1] Since then there have been numerous case reports and a few small series. A review of one of the largest series, comprising 25 women and 28 pregnancies, appeared in 1976.[2] Complications of pregnancy are mainly related to the continuous use of anticoagulants. The increased coagulability normally seen in pregnancy increases the requirement for anticoagulants in women with heart valve prostheses. We report our experience of a large series (51 women, 76 pregnancies) and describe the difficulties associated with the management of pregnancy after heart valve replacement.

## Patients and methods

There have been 76 pregnancies in 51 of 392 women aged <40 years with prosthetic heart valves who have been followed by us at this hospital. There have been 71 deliveries in 47 women, and five women are still pregnant. Patients were aged from 10 to 40 (mean 23 years) at operation. Seven patients were aged less than 15 years. The interval between the operation and first pregnancy ranged from 4 months to 132 months (mean 42 months); two patients had heart valve replacement in the second and third months of pregnancy. Age at conception ranged from 17 to 39 years (mean 25 years). Sixty eight prostheses were inserted (53 Starr-Edwards, seven Björk-Shiley, four Lillehei-Kaster, and a xenograft in four). Twenty eight patients had the mitral valve replaced, seven the aortic valve, 15 had a double valve replacement (either mitral and aortic (10) or mitral and tricuspid (five)), and one patient had a triple valve replacement.

### PREOPERATIVE OBSTETRIC HISTORY

Thirty three women had not been pregnant before operation for heart disease and seven had had an abortion, either induced (two) or spontaneous (five). All but two of the pregnancies occurred without the woman first seeking medical advice. Fifty four pregnancies were reported in the first trimester, 18 in the

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Accepted for publication 24 June 1985

Table *Outcome of 71 pregnancies in women with cardiac valve prostheses*

| | *Heparin only* | *None* | *Oral anticoagulants* | *Total* |
|---|---|---|---|---|
| Spontaneous abortion | 3 | 1 | 8 | 12 |
| Premature deliveries | — | 4 | 8 (two of those lived) | 12 |
| Stillbirths | — | (4) | (3) | 7 |
| Neonatal deaths | — | — | (3) | 3 |
| Normal fullterm deliveries | 2 | 8 | 37 | 47 |
| Total number of pregnancies | 5 | 13 | 53 | 71+(10) |

*Figures in parentheses are already included in one of the events.

second trimester, and two in the third. Two pregnancies went to term without any follow up or treatment.

ANTICOAGULANT TREATMENT

Oral anticoagulants were given during 53 of the 71 pregnancies. The five women who are currently pregnant (three in the fourth month, one in the sixth month, and one in the eighth month) are also on oral anticoagulants. Heparin was used during five pregnancies. No anticoagulants were given in 13 pregnancies: in 10 of these oral anticoagulants were discontinued before pregnancy, in two they were changed to antiplatelet treatment during the second month of pregnancy, and in one an antiplatelet agent was given.

## Results

FETAL COMPLICATIONS

In the five pregnancies in which heparin only was given, there were three spontaneous abortions in the second, third, and fifth months of pregnancy. The other two pregnancies were normal and went to term (Table). Of the 13 pregnancies without anticoagulant treatment, eight resulted in normal deliveries, four in stillbirths after premature delivery, and one in spontaneous abortion. In the 53 pregnancies in which oral anticoagulants were given, there were eight spontaneous abortions in the second, third, and fourth months of pregnancy; of the eight premature deliveries there were three stillbirths, three neonatal deaths, and two infants who lived. There were 37 fullterm normal deliveries in pregnancies in which oral anticoagulants had been replaced by heparin at the start of the ninth month. Thus, the 71 pregnancies resulted in 12 spontaneous abortions (three on heparin, one without anticoagulants, and eight on oral anticoagulants), in 12 premature deliveries with seven stillbirths (four without anticoagulants, three on oral anticoagulants), three neonatal deaths shortly after birth (all on oral anticoagulants), and two living infants; and 47 fullterm deliveries with only one death as a result of gastric haemorrhage (two on heparin, eight without anticoagulants, and 37 on oral anticoagulants). Twenty nine female and eighteen male babies survived. The median birthweight was 3 kg (range 2 to 3·8). Most of the surviving children are too young for progress in school to be assessed; however, none had detectable brain damage, mental retardation, or serious congenital abnormality.

MATERNAL COMPLICATIONS

Seven women had cardiac failure, but it responded to rest, salt restriction, digoxin, and diuretics. There were no haemorrhagic complications in the women on heparin, but two had thromboembolisms. Despite apparently regular and efficient anticoagulant treatment, one patient, aged 20 years, had thrombosis of a Starr-Edwards mitral valve prosthesis 24 hours after delivery of a normal child; reoperation was unsuccessful and the patient died in the immediate postoperative period of cardiogenic shock. Another patient with a Starr-Edwards mitral valve prosthesis had four thromboembolic episodes. The first, during the seventh month of pregnancy, resulted in right hemiplegia. The other three episodes occurred in the second and fourth month of pregnancy and on the sixth day after delivery. This patient was reoperated three weeks after the delivery of a fullterm, normal child. There were fibrin deposits at the base and the top of the prosthesis; three years before, this woman had had a coronary embolus when she temporarily stopped anticoagulant treatment.

There were no thromboembolic episodes in the pregnancies without anticoagulants. Two women had bacterial endocarditis. In one it was caused by *Klebsiella*; it occurred in the sixth month of pregnancy resulting in premature delivery. In the other endocarditis was caused by *Candida albicans*; it occurred a few days before delivery and was resistant to antifungals. The patient was reoperated two months after delivery and died from severe septicaemia.

There were 38 uncomplicated pregnancies in women on oral anticoagulants; four patients died, and 11 had complications (uterine haemorrhage and embolism) which rapidly resolved. Two deaths were caused by bacterial endocarditis 25 days and one month after delivery; one death was due to an obstruction of a Starr-Edwards mitral valve prosthesis a few days after delivery in a patient who was on oral anticoagulants until the beginning of the ninth month of pregnancy and was then on heparin. Heparin was stopped at the start of labour and restarted six hours after delivery. The fourth death occurred in the seventh month of pregnancy in a woman who had a severe haemorrhagic episode due to an excessive dose of anticoagulants; the fetus died in utero.

At delivery pulmonary oedema developed in one patient, this responded rapidly to treatment; seven patients presented with uterine bleeding after delivery: three of them were on heparin and one was on an antiplatelet agent.

## Discussion

It is difficult to predict the outcome of pregnancy in women with artificial heart valves. Cardiac output increases by up to 50% in pregnancy; this is normally achieved by an increase in stroke volume rather than by an increase in heart rate.[3] Like others,[2 4 5] we found that pregnancy in women with heart valve prostheses, even those with triple valve replacement, is usually well tolerated when the heart has a good ventricular reserve, is in sinus rhythm, and has properly functioning valves.[6]

Increases in the concentrations of coagulation factors[4] and a reduction in fibrinolysis in pregnancy[7] add to the risk of thromboembolism associated with the presence of a prosthetic heart valve. The clinical manifestations of thromboembolism associated with artificial heart valves in pregnant women do not differ from those seen in non-pregnant women.[8] The most serious complication that we saw was prosthetic valve thrombosis in three patients, which was fatal in two, despite reoperation in one case. Thrombosis of the artificial valve can be prevented by well controlled anticoagulant treatment. Discontinuation of oral anticoagulants or a change in the anticoagulation regimen in pregnant women, usually at the mother's request to reduce the risk to the fetus, may considerably increase the risk of maternal thromboembolism. In a review of 81 pregnant women with cardiac valve prostheses in which 24 patients stopped anticoagulants before or soon after conception, there were six patients with one or more thromboembolic episode and two deaths; whereas only three of the 57 patients on anticoagulants had embolic complications.[9] In Limet and Grondin's series of seven patients one of three patients in whom anticoagulants were stopped before or early in pregnancy died of pulmonary oedema. Necropsy showed a recent friable thrombus engulfing the struts of the prosthesis. One of the four patients on anticoagulants who took their medications haphazardly had a periprosthetic thrombus which led to pulmonary oedema and a saddle embolus of the bifurcation of the aorta.[9] Our results accord with those of Larrea *et al* who reported that thromboembolic complications were common in mitral valve prostheses.[6] In their study of 38 patients in 47 pregnancies three (7·9%) developed thrombosis of their mechanical valves—two Björk-Shiley mitral valve prostheses thrombosed 72 hours after delivery and one Bjork-Shiley aortic valve prosthesis became thrombosed in the sixteenth week of pregnancy.[6] All three thromboses occurred suddenly during apparently well controlled heparinisation, and without apparent change in the clotting time. Two of our five patients on heparin had thrombosis of a mitral valve prosthesis despite well controlled anticoagulation, and one of the patients on oral anticoagulants died of obstruction of a Starr-Edwards mitral valve prosthesis a few days after delivery: this patient was on oral anticoagulants until the start of the ninth month, she was then treated with heparin which was stopped at the start of labour and restarted six hours after delivery. Five other patients on oral anticoagulants had embolic episodes which rapidly resolved (one peripheral, one coronary, and three cerebrovascular). There were no thromboembolic episodes in any of our patients who were not on anticoagulant treatment during pregnancy.

It is widely believed that discontinuation of anticoagulant treatment increases the risk of systemic embolisation in the mother; on the other hand, their use during early pregnancy, near term and at delivery has been reported to be associated with an increased incidence of fetal malformation, stillbirths, and neonatal deaths from haemorrhage. Oral anticoagulants have small molecules that can cross the placenta and they are known to be teratogenic. In 1949, studies in rabbits by Kraus *et al* indicated that the use of coumarin during pregnancy may endanger the fetus.[10] In 1966 DiSaia reported on the first pregnancy after implantation of a cardiac valve prosthesis; this fullterm infant, born to a mother who had received coumarin treatment in early pregnancy, had severe nasal hypoplasia and bilateral optic atrophy.[1] Shaul and Hall summarised the abnormalities seen in 11 patients who had been exposed prenatally to warfarin derivatives.[11] The most constant features were nasal hypoplasia and stippled epiphyses.[11] Hall *et al* reviewed 24 cases in 1980 and confirmed these findings.[12] Other abnormalities included optic atrophy, cataracts, mental retardation, and flexion contractures.

The critical period for teratogenesis is the sixth to the ninth week of gestation, and this may explain why we did not see malformations in our series. Our patients had not usually been treated with anticoagulants in the first trimester. Fetal loss due to abortion, stillbirth, or premature delivery is another complication of anticoagulant treatment. We and others have established that there is unquestionably an increased risk of fetal loss in pregnant women treated with anticoagulants. This risk is especially high when oral anticoagulants are administered from early pregnancy until term and when the dose of anticoagulant is sufficient to depress the prothrombin concentration even for only two days.[9,13,14] In a large review in 1975 Harrisson and Roschke noted that in 55 pregnancies in which the mother had been receiving an anticoagulant (usually warfarin) throughout pregnancy, fetal wastage was 29%, whereas there was no fetal loss in 14 pregnancies in which no anticoagulants were used.[15] Lutz *et al* reported spontaneous fetal wastage of 56% in pregnancies in which coumarin anticoagulants had been given in the first trimester.[16] Ibarra-Perez *et al* reported nine spontaneous abortions in 25 pregnancies in which oral anticoagulants were used virtually throughout pregnancy.[2] In 1979 we reviewed 133 published cases in which there was 30% fetal wastage (21 abortions and 18 stillbirths); of the 39 fetal losses, only one occurred in a patient who was not on anticoagulants and in 10 women there was an obviously reduced coagulability; 12 of the 18 perinatal deaths occurred when oral anticoagulants were taken until term.[8]

Hirsh *et al* stressed the importance of discontinuing oral anticoagulants before term to allow their elimination by the fetus and the restoration of normal prothrombin time.[17] There is evidence that abortions, stillbirths, and early deaths are caused by placental detachment or internal or cerebral haemorrhage; bleeding may be due to the hypocoagulable state in the fetus,[8] which is very sensitive to anticoagulants because of the immaturity of the liver. Thus the fetal prothrombin time may be considerably prolonged even when that of the mother is normal.[18] To avoid bleeding complications in the fetus, maternal prothrombin times should be maintained in the low normal range. There is evidence that heparin does not cross the placenta and therefore it is unlikely to be teratogenic.[18] Administration and monitoring of treatment are difficult, however, and fetal and maternal haemorrhage may occur. The maternal complication rate was high in a series of 135 cases. Fourteen patients (10%) had a haemorrhage and three (2%) of them died.[12] Thirty three per cent of deliveries were premature or stillbirths. Heparin may be substituted for oral anticoagulants in pregnant women with heart valve prostheses, but this change can only be purposefully instituted when the pregnancy is recognised early and before the most vulnerable period for the fetus.

## Conclusions

The risk of heart failure during pregnancy in women with heart valve prostheses is usually not great when bed rest and appropriate medical treatment are feasible; however, patients in functional class III and IV of the New York Heart Association classification with large left atrium and atrial fibrillation should be advised against pregnancy. Such patients are, however, not often encountered because most of them will have had surgical treatment before pregnancy in order to prevent deterioration of cardiac function.

The maternal risk of thromboembolism is high and it is not always prevented by anticoagulants. We found that heparin was less effective than oral anticoagulants and we did not find any teratogenic effects associated with oral anticoagulants. So, although many prefer to use heparin in the first trimester of pregnancy, we do not think that this is justified, even when pregnancy is diagnosed sufficiently early or is planned for. We do, however, recommend the use of heparin at the end of pregnancy to reduce the risk of haemorrhage during labour and delivery. Mothers on anticoagulants are often advised against breast feeding; however, there is evidence that those on warfarin may safely breast feed their infants.[19]

Because of the difficulties encountered in the management of pregnant women with artificial heart valves, some workers strongly recommend the use of bioprosthetic heart valves in women of child bearing age; but we believe that this attempt to reduce the risk of rapid valve failure is justified only in patients in sinus rhythm who are >25 years old.

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*Br Heart J* 1986; **55:** 106–8

# *Case reports*

# Aortic dissection during pregnancy

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SUMMARY Aortic dissection occurred in a nineteen year old woman during the thirty seventh week of pregnancy. Immediate elective delivery of a normal baby by caesarean section was followed by aortic root replacement 48 hours later. It was decided not to proceed immediately to operation on the aortic root because it was believed that the anticoagulation necessary for cardiopulmonary bypass might provoke dangerous haemorrhage from the raw placental site.

## Case report

A nineteen year old woman booked in for her first pregnancy at the local hospital. She remained well and fetal growth was normal until the thirty seventh week when she complained to her general practitioner of dizziness and a discomfort in her neck and chest radiating through to her back. Clinical examination at that time was normal. Two days later, however, her husband noted vibration in her chest and the family doctor confirmed the presence of new cardiac murmurs.

She was admitted to the local district hospital, and one week later was referred to the regional centre. On admission she had mild chest discomfort and tiredness. Clinical examination showed no signs of heart failure. She was normotensive with a blood pressure in both arms of 105/55 mm Hg. A systolic thrill was present to the right of the upper part of the sternum, and on auscultation an ejection systolic and early diastolic murmur were heard.

A chest radiograph showed an enlarged cardiac shadow but the upper mediastinum was normal (Fig. 1). The electrocardiogram was normal. Cross sectional ultrasound examination showed that the aortic root was 7 cm in diameter; in the short axis view the aortic root was shown to consist of a normal sized main lumen with a large false lumen on the right side (Fig. 2).

Labour was avoided to protect the mother from the possible extension of the presumed aortic dissection, and a normal baby was delivered by elective caesarean section within 24 hours of admission. Aortography three hours after operation confirmed the diagnosis of a dissecting haematoma confined to the ascending aorta and gross aortic incompetence.

We decided not to proceed to immediate operation on the aortic root because we believed that, as the uterus had only partly contracted, the anti-

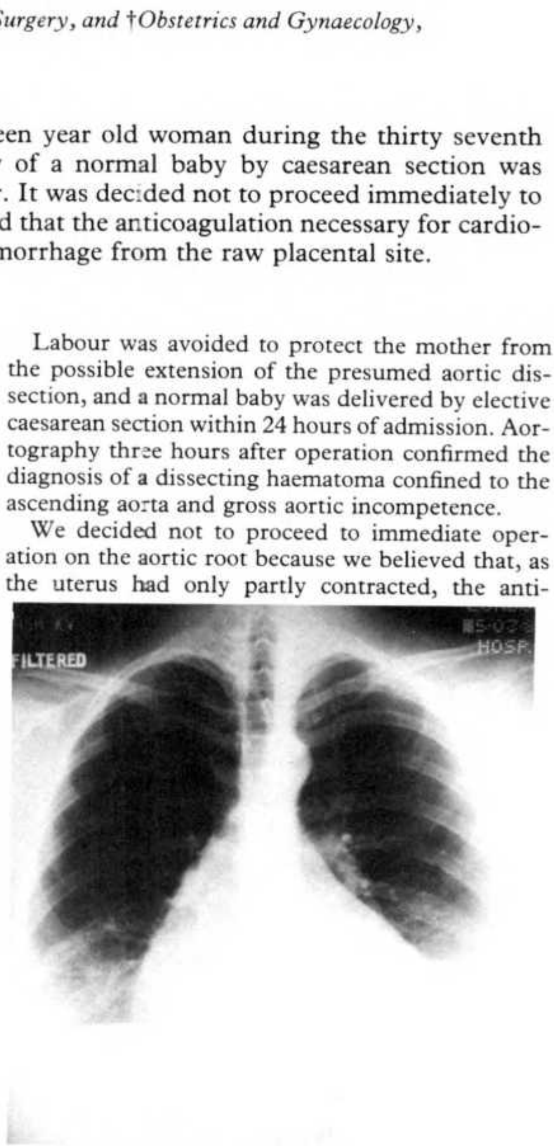

Fig. 1 *Chest radiograph at admission.*

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coagulation necessary for cardiopulmonary bypass might provoke dangerous haemorrhage from the raw placental site. To avoid increasing the patient's blood pressure oxytocin had not been given. Arterial hypotension was maintained by sodium nitroprusside infusion for 48 hours to allow healing of the uterus. Then the ascending aorta was replaced by a Dacron prosthesis containing a Björk-Shiley valve with reimplantation of the coronary arteries. Her postoperative recovery was uneventful apart from persistent symptomatic atrioventricular dissociation for which a permanent pacemaker was inserted. At follow up two months later mother and baby were well.

Examination of the aortic root showed an intimal tear, 3 cm above a bicuspid aortic valve, giving rise to a large dissecting haematoma with no exit point. The histology of the aortic wall was normal with no evidence of cystic degeneration.

## Discussion

Most aortic dissections occur as a result of systemic hypertension[1]; indeed it has been argued that if systemic hypertension were eliminated, spontaneous aortic dissection would virtually disappear.[2] Other risk factors, such as Marfan's syndrome, trauma,[3] the presence of a bicuspid aortic valve,[4 5] and pregnancy,[6-8] have been identified.

Dissection of the aorta in pregnancy is very rare, and usually occurs in the third trimester when blood volume and cardiac output are rising to a maximum.[7] It has been known to occur at all stages of pregnancy and during the weeks after delivery.[8] Primiparous patients seem more susceptible. In one report, 50% of aortic dissections in women of child-bearing age occurred during pregnancy,[8] but in many of these cases the blood pressure was not documented. Therefore it may be that the systemic hypertension associated with many pregnancies, especially the first pregnancy, is responsible for the high frequency of dissections in pregnant females compared with non-pregnant females of the same age.[2]

The patient reported here was known to have had normal blood pressure throughout her pregnancy. She had a bicuspid aortic valve, however, which is also known to be associated with aortic dissection.[4 5 9] In two necropsy series, bicuspid valves were found in 10% of cases of dissection.[4 9] Dissection of the ascending aorta is as common in non-stenotic valves as in those causing important obstruction,[10] so a generalised structural disorder of the arterial wall,[2 11] rather than haemodynamic stress[12] is likely to be responsible.

The histological appearance of the aortic wall in the patient reported here was normal. Cystic medionecrosis is commonly described in cases of dissection, especially in pregnancy,[8] but the wide range of its reported incidence reflects a considerable difference in the diagnostic criteria used by pathologists.[13] True cystic medionecrosis probably only leads to dissection in Marfan's syndrome (which accounts for only three per cent of cases of dissections), and other changes labelled cystic medionecrosis, which are often neither cystic nor necrotic, are non-specific and commonly found in aortas routinely examined at necropsy.[13] Histologi-

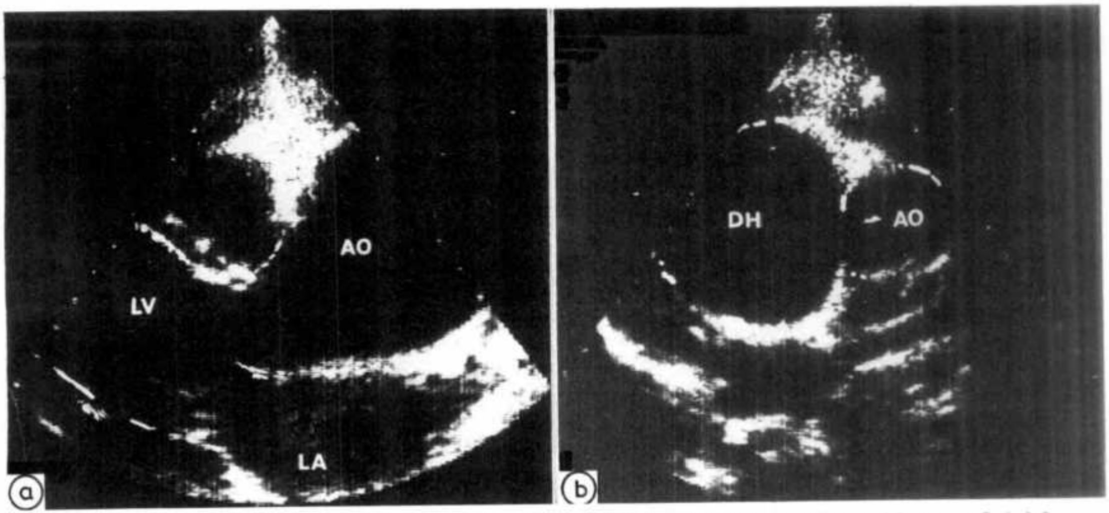

Fig. 2 *Cross sectional echocardiographic long axis (a) and short axis (b) views of the aortic root. AO, aorta; LA, left atrium; LV, left ventricle; DH, dissecting haematoma.*

cal examination will not show the subcellular and chemical changes which are thought to occur in the connective tissue during pregnancy as a result of alterations in lipid metabolism and the high serum concentrations of oestrogen.[13] A combination of these ultrastructural changes together with a congenital weakness of the aorta associated with a bicuspid aortic valve may have led to this patient's aortic dissection.

Elective caesarean section was the preferred method of delivery. Discussion centred on how much time should be allowed for healing of the placental site in the uterus before proceeding to surgery on the aortic root. The risk of severe haemorrhage from the fresh placental site had to be balanced against the risk of rupture of the aortic wall. Dissection had occurred some days before the patient arrived in our hospital, and, as ischaemic pressure necrosis of the outer aortic wall can develop at any time, the state of her aorta was always felt to be precarious. As a compromise we waited 48 hours and maintained hypotension ($<95$ mm Hg systolic) with sodium nitroprusside infusion. In the event there was no postoperative uterine bleeding.

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*Br Heart J* 1986; 55: 109–11

# Severe mitral regurgitation in a woman with a double orifice mitral valve

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SUMMARY A 64 year old woman with partial atrioventricular canal and double orifice mitral valve presented with severe mitral regurgitation secondary to a torn leaflet. The double orifice regurgitant mitral valve is an unusual finding at operation.

Double orifice mitral valve is an unusual congenital abnormality that is rarely of clinical importance. We describe a patient in whom this finding was associated with severe mitral regurgitation.

## Case report

A 64 year old woman was noted to have a murmur at age 20, but was symptom free until 1977 when congestive heart failure developed. A murmur typical of mitral regurgitation was noted. Her symptoms resolved on digoxin and diuretic treatment. She did well until November, 1983, when symptoms of weakness, abdominal distension, dyspnoea, and palpitation developed. Frusemide and quinidine (for ventricular extrasystoles) were started but when her symptoms progressed she was referred to our institution.

### CLINICAL FINDINGS

Physical examination showed a normotensive female in no distress. Pulse was 66 beats per minute with frequent extrasystoles. Her venous pressure was raised with pronounced V waves. Carotid pulses were normal. The apical impulse was felt in the sixth intercostal space in the midclavicular line, and there was a left parasternal thrill. The first and second heart sounds were normal. The third heart sound was soft. A grade 5/6 harsh pansystolic murmur radiated from the heart apex to the axilla and spine. There was a grade 3/6 harsh systolic murmur at the left sternal border. There was a soft diastolic murmur at the apex. A pulsatile liver was palpable 5 cm below the right costal margin. There was minimal oedema.

The electrocardiogram showed left axis deviation, first degree atrioventricular block, and right bundle branch block. A chest *x* ray film showed cardiomegaly, prominent pulmonary arteries, and increased pulmonary vascular flow. Laboratory studies were unremarkable.

Cross sectional echocardiography (Fig. 1) showed left atrial, right atrial, and right ventricular enlargement; an ostium primum type atrial septal defect; and a cleft anterior mitral leaflet. A contrast study demonstrated right to left shunting across the atrial septal defect. At retrospective examination of the echocardiogram two separate mitral valve orifices could be seen in the parasternal long axis right ventricular inflow view.

Cardiac catheterisation demonstrated raised right heart pressures, increased right atrial oxygen saturation and mild arterial desaturation. The pulmonary: systemic blood flow ratio was 1·9:1.

Left ventricular cineangiography showed normal wall motion with evidence of a gooseneck deformity of the left ventricular outflow tract and severe mitral regurgitation. There was left atrial and right ventricular enlargement. Early appearance of contrast in the right atrium confirmed the presence of an atrial septal defect. Coronary angiography was normal.

### FINDINGS AT OPERATION

The heart was explored through a lateral right atrial incision. The tricuspid valve annulus was considerably dilated with a cleft in the septal leaflet extending to the septal rim. The valve was grossly incompetent. A 3 cm diameter ostium primum defect was present. The mitral valve was fully viewed through an incision in the atrial septum (Fig.

Requests for reprints to Dr Jack Kron, Department of Medicine, Division of Cardiology, Oregon Health Sciences University, 3181 SW Sam Jackson Park Road, Portland, Oregon 97201, USA.

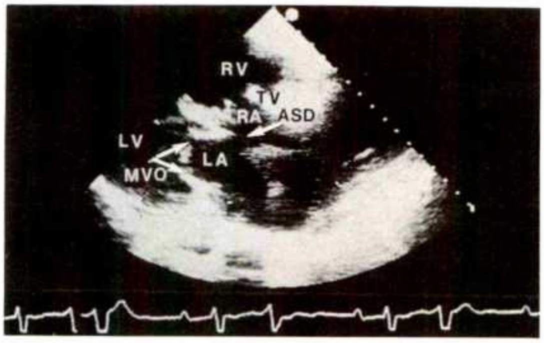

Fig. 1 *Cross sectional echocardiogram (parasternal long axis, right ventricular inflow view) showing both the atrial septal defect (ASD) and the dual orifice mitral valve. LA, left atrium; LV, left ventricle; MVO, mitral valve orifice; RA, right atrium; RV, right ventricle; TV, tricuspid valve.*

2). It was composed of an oval annulus with two complete orifices divided by a transverse bridge of leaflet tissue. Each orifice had its own slightly eccentric placed papillary muscle. From each muscle, chordae tendineae radiated in a parachute fashion to the leaflet edges. The posterior orifice was approximately two thirds the diameter of the anterior orifice and was fully competent. The anterior orifice had a cleft in its anterior leaflet opposite the cleft in the septal leaflet of the tricuspid valve. On the anterior ostial margin of the cleft there was a single ruptured chord and a thickened flail leaflet. A regurgitant jet was demonstrated in this segment when the left ventricle was filled with saline solution.

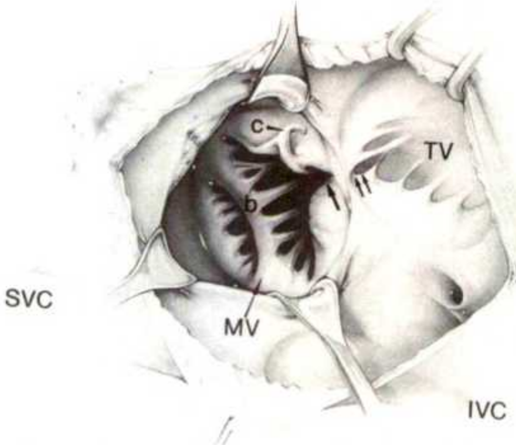

Fig. 2 *Drawing of the in situ surgical findings. The mitral valve is viewed at operation through a surgically enlarged ostium primum atrial septal defect via a right atrial incision. Mitral valve (MV) with torn chord (c) and cleft anterior leaflet (large arrow) and bridging tissue (b). TV, tricuspid valve with cleft septal leaflet (small arrows). SVC, superior vena cava. IVC, inferior vena cava.*

Repair of the ruptured chord by reimplantation did not restore valve competence. Cleft closure with interrupted sutures also failed to restore complete competence. We considered closure of the larger orifice, but believed that the secondary orifice would be inadequate to maintain flow. Therefore both mitral valve orifices were excised and were replaced with a 3M Starr-Edwards 6120 valve. The cleft in the septal leaflet of the tricuspid valve was closed. Tricuspid competency was restored by re-establishing a near normal annular shape and size by use of a 28 mm Carpentier tricuspid ring. The ostium primum defect was closed with a patch of autogenous pericardium secured by running suture.

## Discussion

Double orifice mitral valve is a rare disorder that was first reported by Greenfield in 1876[1]; over sixty cases have since been described.[2-13] This abnormality is rarely of clinical importance,[7] and most cases are recognised at operation or necropsy. It occurs as an isolated lesion or in association with other anomalies such as atrioventricular canal, bicuspid aortic valve, coarctation of the aorta, transposition of the great arteries, patent ductus arteriosus, supravalvar mitral stenosis, subaortic stenosis, secundum atrial septal defect, and ventricular septal defect.[3,4,6,10,13] Endocardial cushion defects are present in 25–50% of cases,[4,7,14] with double orifice mitral valve being seen in 3–10% of all cases of persistent atrioventricular canal.[3,13,14] The case we describe is unusual because of the patient's age and mode of presentation. The oldest patient in the Wakai and Edwards necropsy study was 13 years old and all the others were $<2\frac{1}{2}$ years old.[3] In the largest series reported all patients were $\leqslant 20$, and the double orifice valve was generally an incidental finding.[13] Clinically important mitral regurgitation[5,6,9,15] has been diagnosed on the basis of a geometrically deformed valve,[9] anterior mitral leaflet fenestration,[5] or abnormal origin of the chordae tendineae and papillary muscles.[6] This is the first report of a case in which a flail leaflet due to a ruptured chorda tendineae caused severe mitral regurgitation.

### ANATOMICAL AND EMBRYOLOGICAL FEATURES

Ilbawi *et al* reported eight patients with double orifice mitral valves.[14] Four had an intermediate atrioventricular canal without a cleft mitral leaflet while the others had ostium primum defects. The former group had intractable congestive heart failure and did not survive operation, whereas the latter group recovered. These findings accord with those in a later series.[3 13] All five of the cases in the Wakai and Edwards series were associated with complete or intermediate atrioventricular canals and all the patients died of congestive heart failure or postoperatively.[3] The 11 cases in the Warnes and Somerville series were associated with ostium primum defects and tended to have a better course.[13] This resembles our patient, who first presented in her fifties.

There is some disagreement about the embryological origin of this lesion. Wimsatt believed that the accessory orifice was the result of abnormal fusion between the anlagen of the medial and lateral mitral valve leaflets.[16] Lewis, however, believed that the accessory orifice was the result of developmental arrest and persistence of the left part of the common atrioventricular canal, resulting in an accessory orifice in tissue destined to become a mitral leaflet.[16] Ancalmo *et al* supported the latter theory because endocardial cushion defects are often found in association with this lesion.[7]

## ANGIOGRAPHIC AND ECHOCARDIOGRAPHIC FINDINGS

Our patient showed the typical gooseneck deformity of the subaortic region of the left ventricle seen in ostium primum defects caused by abnormal placement of the anterior mitral leaflet.[17 18] Warnes and Somerville and Somerville and Jefferson have described two rows of fine crenations in the medial region of the left ventricle, representing the double orifice.[13 18] Echocardiography will often define both orifices.[14 18] If an ostium primum defect is present, the fishmouth appearance of the normal mitral valve is replaced by a triangular configuration with separation of the anterior components of the anterior leaflet. Although the double orifice was not recognised before operation in our patient, on retrospective examination of the echocardiogram the angulated parasternal long axis view showed two orifices (Fig. 1).

## SURGICAL CONSIDERATIONS

The surgical approach to patients with mitral valve abnormalities associated with endocardial cushion defects has recently been reviewed.[14 19] Our approach resembles that of the Mayo Clinic group.[20] It has been our experience that when the cleft in the mitral valve has been left intact, or only partly closed, reoperation has been required because of progressive mitral regurgitation.[19] Therefore, we usually close the cleft with interrupted sutures if the mural leaflet component of the mitral valve is of adequate size (that is, greater than one third of the circumference of the annulus). In cases where the mural leaflet component is less developed, the cleft has been left partly or completely open; however, as noted earlier, this has given less than satisfactory results. In cases where the cleft is left open, invagination of the base of the commissure may provide better apposition and competence. If not, mitral valve replacement is probably indicated.

Double orifice mitral valve is a rare lesion that can complicate the surgical repair of endocardial cushion defects.[14 18] Diagnosis should be considered in patients who have evidence of an ostium primum atrial septal defect. Cross sectional echocardiography and left ventricular angiography can be useful in establishing the diagnosis.

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*Br Heart J* 1986; 55: 112-4

## *Correspondence*

# Abrupt withdrawal of atenolol in patients with severe angina: comparison with the effects of treatment

Sir,
I have read the report by Walker *et al* (1985; 53: 276-82) on the results of a study on the effect of atenolol withdrawal in patients with chronic stable angina pectoris. As a result of their findings, they came to the rather dangerous conclusion that atenolol withdrawal can be expected to carry no appreciable risk of precipitating a coronary event in patients with little or no angina.

In 1979, Meinertz *et al* suggested that the abrupt discontinuation of any beta blocking agent should be expected to produce a withdrawal syndrome similar to that described for propranolol.[1] The point at which rebound phenomena occur can be delayed for as long as 21 days after withdrawal[2-4]; the duration of the study performed by Walker *et al* was therefore too short to permit a conclusion that atenolol is devoid of this risk. Furthermore, in a different study, there was evidence of rebound withdrawal phenomena in two of 14 patients after substitution of atenolol by placebo.[5] Others have shown no difference between the beta blockers propranolol, oxprenolol, atenolol, and acebutolol in their propensity to cause a rebound increase of heart rate under conditions of increased sympathetic drive after withdrawal.[6] The statement that atenolol has not yet been associated with a withdrawal syndrome is therefore incorrect.

Clearly there is a great deal of variability in the appearance of the beta blocker withdrawal syndrome and advice that treatment with any beta blocker should be withdrawn gradually, irrespective of the disease under treatment, still stands.

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1 Meinertz T, Just H, Kasper W, Kersting F, Breuing K-H. β-blocker withdrawal syndrome? *Lancet* 1979; i: 270.
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This letter was shown to Dr Walker, who replies as follows:

Sir,
While we respect Dr Ashford's concern regarding the potential ill effects of abrupt beta blockade withdrawal we maintain that our results justify our conclusions. The suggestion of Meinertz *et al* was an extrapolation from one case (which concerned metoprolol),[1] while the contention that rebound phenomena can occur as late as 21 days after withdrawal is based on just two patients, both of whom had developed unstable angina within 24 hours of propranolol withdrawal.[2] Among 21 cases of the "propranolol withdrawal syndrome" in whom the timing of events was stated all but three occurred within seven days of withdrawal.[2-5] Rebound adrenergic hypersensitivity—when it has been demonstrated[6,7]—has always been maximal within seven days. Hence it cannot be confidently stated that these late events were rebound phenomena. While we accepted in our paper that our post-withdrawal period might ideally have been longer than 144 hours, it nevertheless included that time during which other workers have demonstrated rebound hypersensitivity under conditions of increased sympathetic drive.[7]

Our statement that "atenolol has not as yet been associated with a withdrawal syndrome" is to our knowledge correct according to the definition which we and others have applied[8]: that is, one inclusive of serious coronary events. The two (hypertensive) patients mentioned by Dr Ashford had no cardiac symptoms. Our data also showed that abrupt withdrawal of atenolol produces a gradual loss of beta blockade, which is why a gradual reduction in dosage is unnecessary.

We have attempted to avoid the rather anecdotal and speculative discussion which tends to surround the "beta blockade withdrawal syndrome", confining our conclusions to the specific agent and clinical setting tested. If it can ever be considered reasonable to withdraw a beta blocker then based on our data in patients with severe stable angina it should surely not be considered a "dangerous" practice to stop treatment with atenolol in patients who have mild or no symptoms?

P R Walker,
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# Effect of timolol on changes in serum potassium concentration during acute myocardial infarction

Sir,
Nordrehaug *et al* (1985; **53:** 388–93) showed that the administration of timolol after myocardial infarction reduces the frequency of hypokalaemia during the first 24 hours after the infarct. For greater accuracy they should have used plasma rather than serum because there is erratic leakage from erythrocytes during coagulation.

Using insulin-induced hypoglycaemia (in healthy volunteers) as another model for acute stress, we have also observed that prior non-specific beta blockade with nadolol or propranolol prevents hypokalaemia.[1 2] Since these effects of stress are mediated through a pronounced increase in plasma catecholamine concentrations it is pertinent to mention that adrenaline-induced influx of potassium into leucocytes in vitro is inhibited by the non-selective beta blocker, timolol and that these cells are probably a model for body cells as a whole.[3] In addition, beta blockade in the hypoglycaemia model[1] reduces the magnitude of (*a*) increase in serum free fatty acid concentrations by inhibiting lipolysis; (*b*) the increase in various haemostatic variables like factor VIII related antigen; (*c*) platelet aggregation. These effects are related to the pathogenesis of myocardial infarction since they are all arrhythmogenic or prothrombotic.[4–6] It is also important to determine whether selective blockade of $\text{beta}_1$ receptors produces similar results since some of the above effects of catecholamines are thought to be mainly mediated by $\text{beta}_2$ receptors.

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**References**

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# A case of fatal peripartum cardiomyopathy

Sir,
In 1970 you published a report by myself and colleagues from this hospital on a case of fatal peripartum cardiomyopathy.[1] Since then, our patient's younger sister has died at the age of 31 at another hospital of dilated cardiomyopathy. An older sister developed congestive heart failure after delivery of a son at the age of 38 but she recovered. This son developed congestive heart failure at the age of 12 and was investigated by paediatricians at this hospital. He was found to have a dilated cardiomyopathy associated with serological evidence of recent Coxsackie virus infection and has been treated by cardiac transplantation. His younger brother developed heart failure attributed to cardiomyopathy and died nearly two years after operation for closure of persistent ductus. The case of the 12 year old boy will be reported by Dr Rosemary Rayner who will describe the family history and discuss the interrelation of genetic and environmental factors in the genesis of dilated cardiomyopathy.

In our original article we stated that in our patient's case there was no family history of heart disease. The purpose of this letter is to correct this statement retrospectively, in the light of these later developments.

M Honey,
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**Reference**

1 Hughes RAC, Kapur P, Sutton GC, Honey M. A case of fatal peri-partum cardiomyopathy. *Br Heart J* 1970; 32: 272–6.

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# *Notices*

## Electrocardiology in Amsterdam

A symposium in honour of the late Professor Dirk Durrer on 35 Years of Electrocardiology in Amsterdam will be held at the Royal Tropical Institute, Amsterdam, on 29 and 30 May 1986. Further information may be obtained from: Dr Frits L Meijler, Interuniversity Cardiology Institute, Catharijnesingel 101, 3511 GV Utrecht, The Netherlands.

## British Cardiac Society

The Annual General Meeting for 1986 will take place in York on 2 and 3 April 1986, and the closing date for receipt of abstracts will be 2 January 1986.

*Br Heart J* 1986; **55:** 115–6

# CHECKLIST

## *Please make a photocopy of this checklist, complete, and send with all manuscripts submitted for publication.*

**General**

☐Two complete sets of the manuscript (including 2 sets of figures) are submitted.

☐The manuscript is typed double spaced throughout on one side only on 22 × 28 cm (8½ × 11″) opaque white bond paper with 3 cm margins all around.

☐The manuscript is arranged as follows: (1) title page, (2) summary, (3) text, (4) references (5) legends, (6) tables. Pages are numbered consecutively, beginning with the title page as page 1.

☐The last name of the first author is typed at the top right corner of each page.

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☐The title and authors' names with symbols (* † ‡ etc) to indicate place of appointment are typed on the title page.

☐No more than three authors' names are given for case reports.

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**Text**

☐Abbreviations or acronyms are always written out in full (for example, ECG, electrocardiogram; LVH, left ventricular hypertrophy; CAD, coronary artery disease, MI, myocardial infarction).

☐Only units of measurement and mathematical formulas and calculations are abbreviated and they follow the form recommended in *Uniform Requirements for Manuscripts Submitted to Biomedical Journals* (*Br Heart J* 1984; **51:** 1–6).

☐Appropriate headings and subheadings are provided.

☐Every reference, figure, and table is cited in the text in numerical order. (Order of mention in text determines the number given to each.)

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**References**

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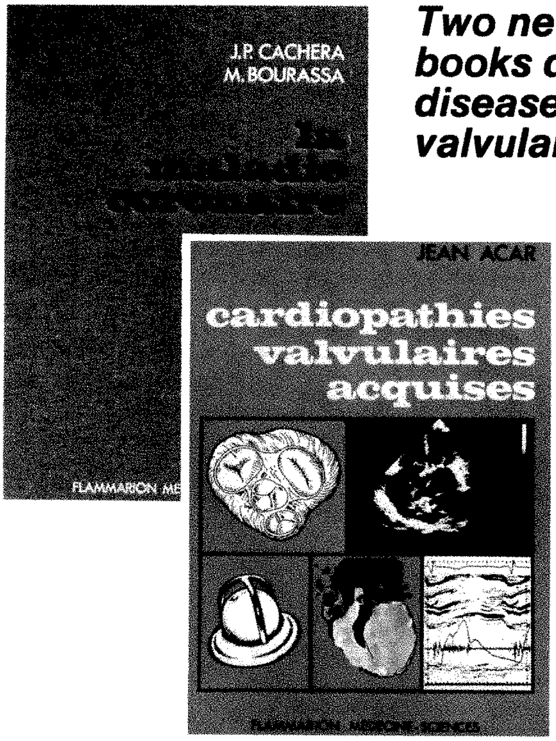

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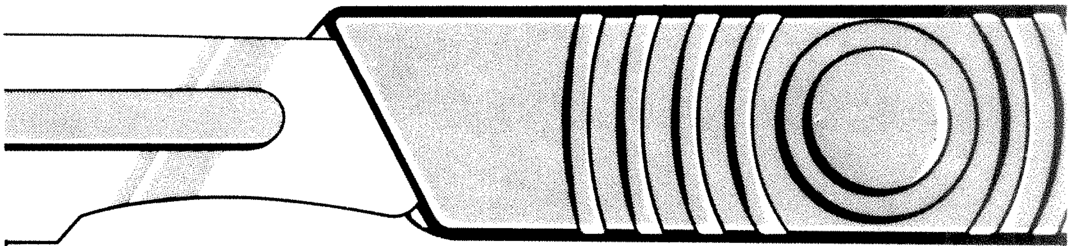

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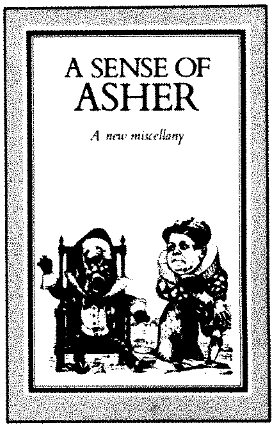

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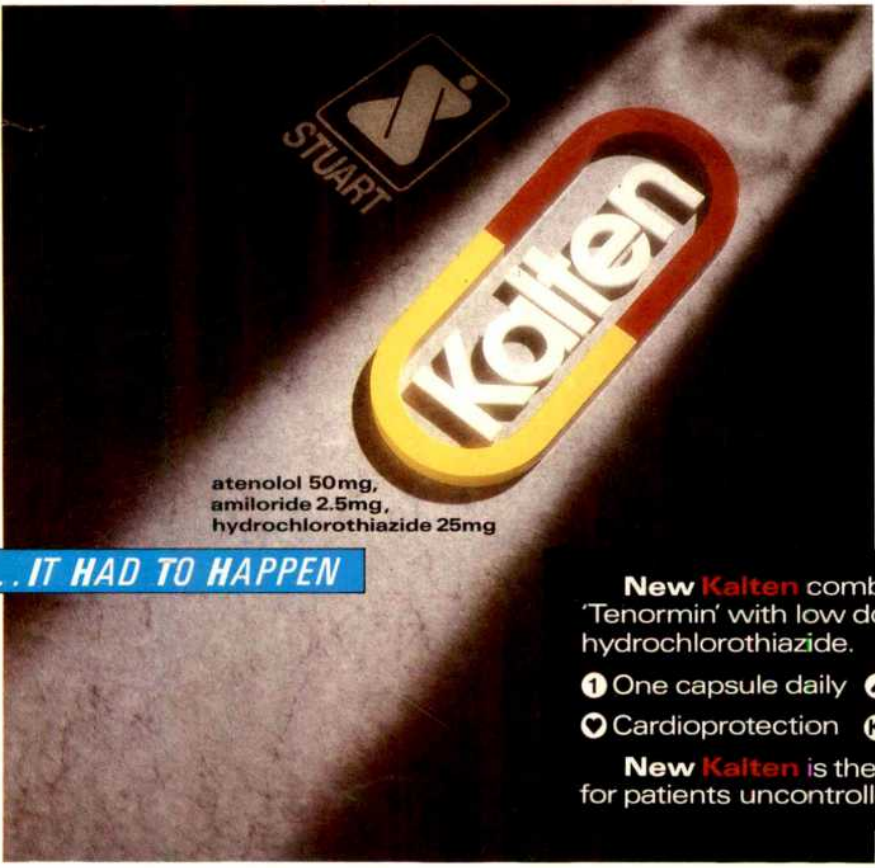

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ASTM CODEN: BHJUAV 55(2) 117—220 (1986)
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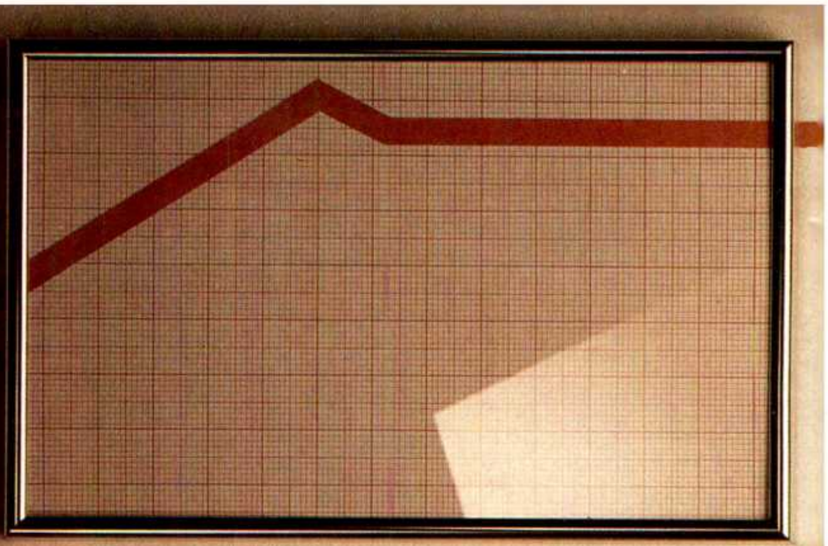

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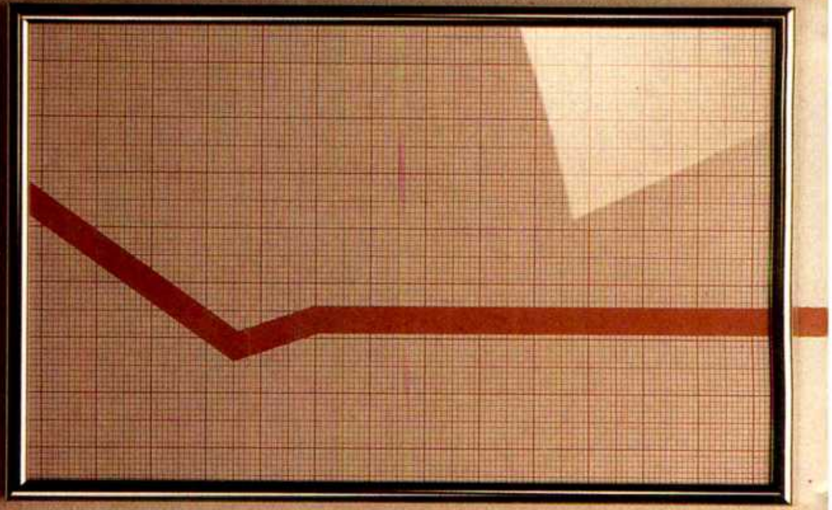

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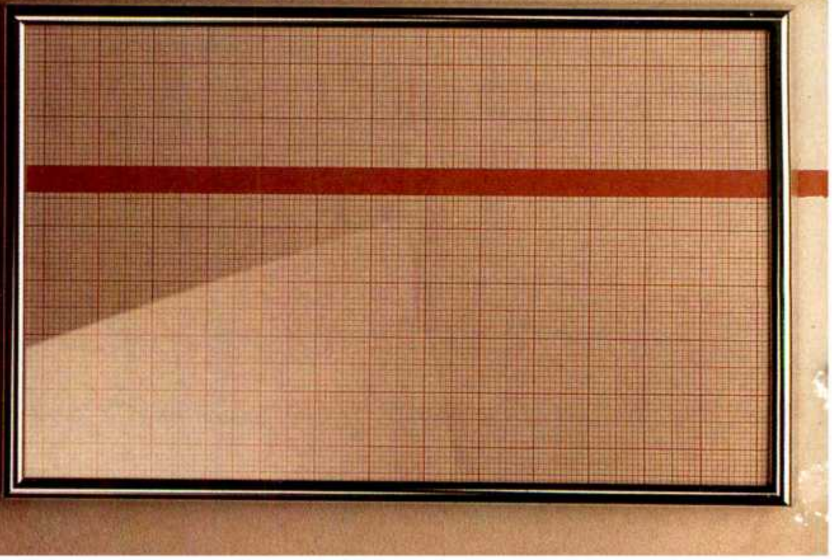

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**References**

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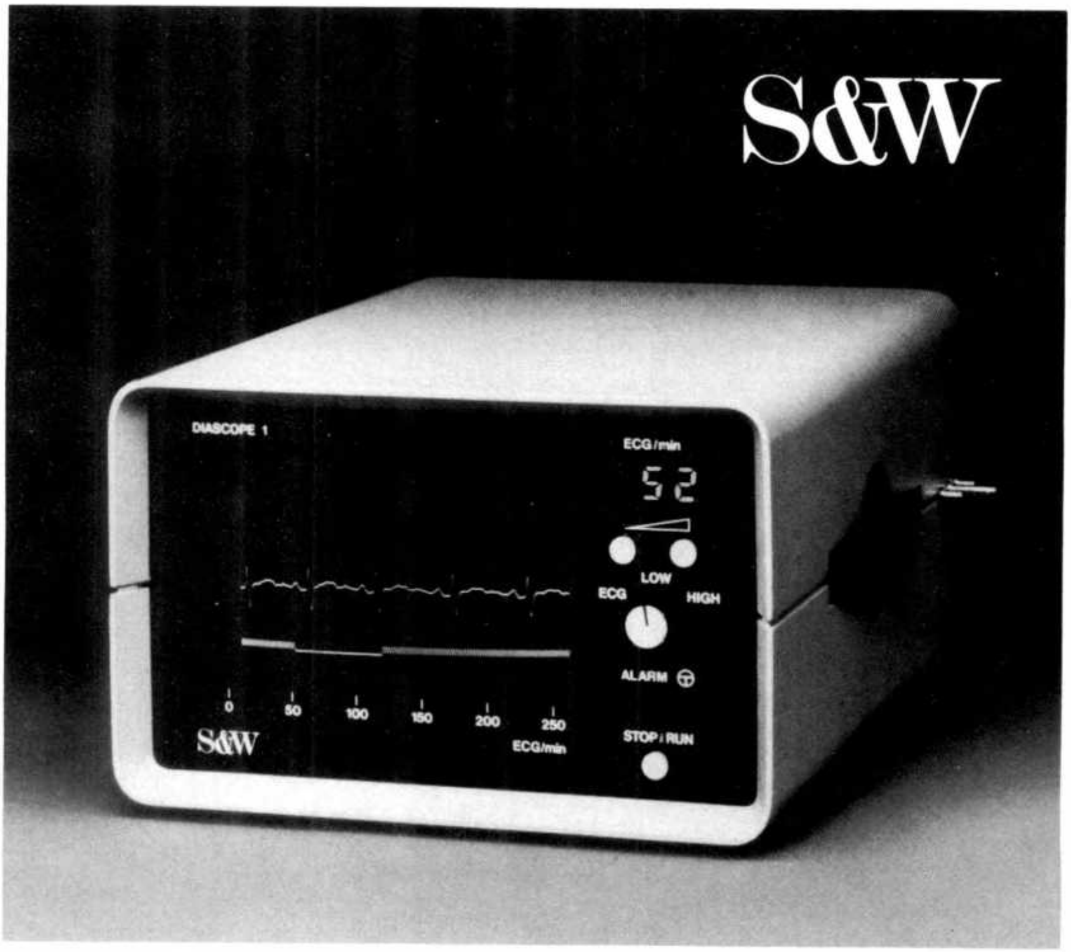

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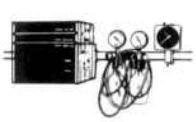
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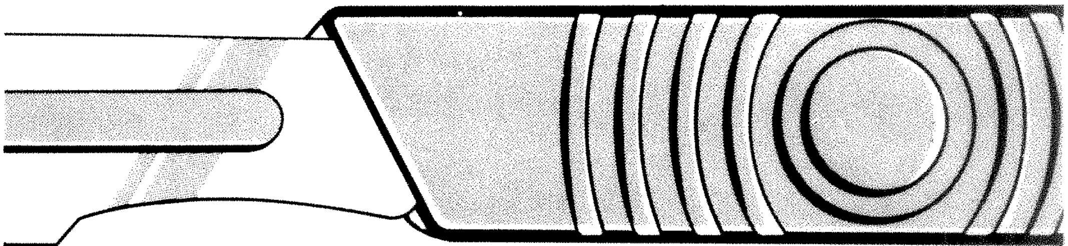

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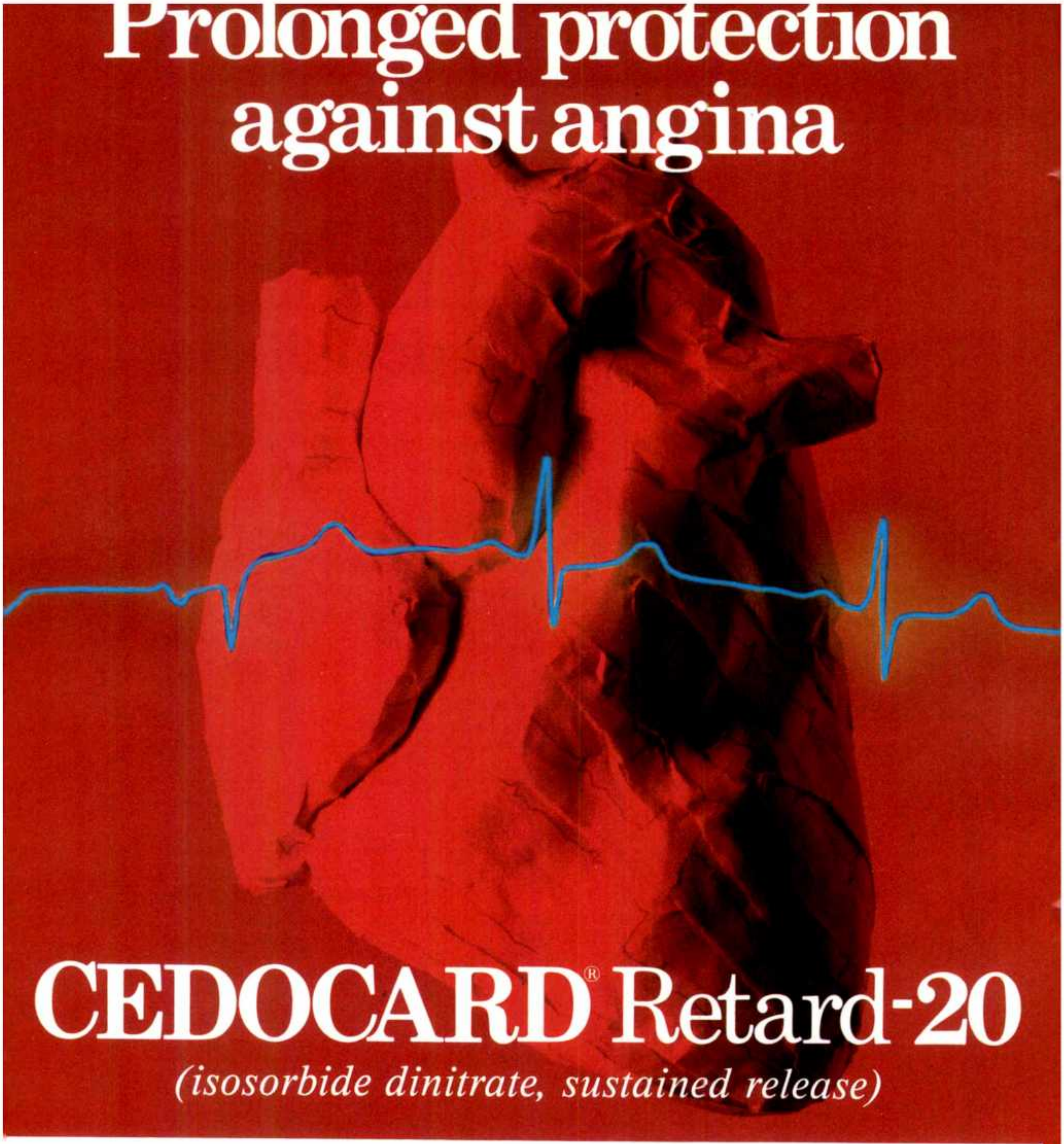
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*Br Heart J* 1986; 55: 117–9

*Editorial*

# Assessing the severity of valve stenosis

O ODEMUYIWA, R J C HALL

*From the Department of Cardiology, Royal Victoria Infirmary, Newcastle upon Tyne*

In the early days of cardiac catheterisation the pressure gradient was the main criterion for the estimation of the severity of valve stenosis. The gradient alone, however, is not a true reflection of stenosis since it is heavily dependent on the cardiac output and heart rate. Thus its use can lead to gross errors in the diagnosis of those severe valve lesions that considerably reduce cardiac output and hence produce only a small gradient. This situation is not uncommon in end stage aortic stenosis, a condition in which correct diagnosis is essential because surgery can be life saving.[1] Increases of left ventricular end diastolic pressure can confound mitral valve gradient measurements and also lead to underestimation of severity even by experienced investigators.[2] A major advance in the assessment of valve stenosis came in 1951 when Gorlin and Gorlin derived the formula which related heart rate, pressure gradient, and cardiac output to valve area.[3] Several sources of inaccuracy became apparent as use of this formula increased. The hydraulic equations from which the Gorlin formula was derived assume flow through an idealised orifice and not through the funnel shaped spout of a stenotic mitral valve. There are also theoretical deficiencies in the use of the square root of the mean pressure gradient instead of the mean square root of the instantaneous pressure gradients.[4] The formula depends on the accurate measurement of cardiac output, but each application of the Fick principle to this measurement has its unique sources of imprecision. Accurate pressure measurements are also important, and significant errors can be introduced first in the measurement of the pulmonary artery wedge pressure itself and also in its use as a substitute for left atrial pressure.[5] The Gorlin formula is also misleading in the presence of important regurgitation. Lastly the formula was verified by digital palpation at operation or in necropsy specimens neither of which could accurately represent valve dimensions in life.

The sources of inaccuracy in the Gorlin formula have been tackled either by direct measurements or indirectly by a mathematical approach. Valve areas have been measured directly with templates or sizers.[6] These have been quite successful with the mitral valve, although there is uncertainty about the change in shape and size of an excised mitral valve without its subvalvar apparatus. Aortic valves are more difficult because they tend to be forced open, fragment, or crack during sizing. The indirect mathematical approach is to try to derive new and more accurate equations based on solid theoretical foundations and more certain corroboration. A recent equation[7] eliminates the diastolic filling period and uses a new constant, but it remains to be seen whether these will compensate for the limitations of measuring cardiac output and pressure.

Although the validity of catheter data has largely been accepted without question it is apparent that the assumptions which underpin correlative studies are not true. The components of the so-called gold standard are themselves not made of gold and the quality of the standard must vary both between and within centres. Despite these limitations cardiac catheterisation has been central to the increasing understanding of the pathophysiology of cardiovascular disease, and by serving as a reasonably reliable reference has spurred improvements in cardiac surgery and the interpretation of physical signs. Cardiac catheterisation is however expensive, time consuming, and sometimes dangerous,[8] and therefore as non-invasive techniques have improved the focus has shifted to their use in assessing valve stenosis. These techniques usually evoke an initial enthusiasm that is followed by disappointment until some middle ground is found between these extremes.

Echocardiography is the most useful and thoroughly investigated of the non-invasive techniques. Early work on mitral stenosis examined particular variables in relation to findings at cardiac catheterisation or operation, and indices of severity such as the diastolic closure rate,[9] mitral valve closure index,[10] and changes in left ventricular

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dimensions[11 12] were derived. These indices went through the usual sequence of evaluation and detailed study[13] and were often the subject of acrimonious debate. In some eyes these and other studies like them confirmed the echocardiogram as a potential replacement for cardiac catheterisation,[14] but others believe that the catheter laboratory is still the only source of accurate information.[15] It was not clear how often the echocardiogram provided information not available from the clinical examination and simple tests (such as the electrocardiogram and chest *x* ray) and made a contribution to decisions about operation without catheterisation. This is important because as non-invasive techniques proliferate there is a tendency for patients to undergo an increasing number of investigations before the inevitable ritual of catheterisation. One approach has been to simulate the diagnostic cascade.[16-18] It is estimated that about 70% of patients investigated for valve surgery may not need catheterisation because mild and severe disease could be accurately defined non-invasively. These studies also highlighted some of the difficulties such as the tendency for the echocardiogram to overestimate aortic stenois[18] and the limitations of echocardiographic assessment of moderately severe mixed or multiple lesions. This latter category has proved the most difficult to assess by any of the current techniques including catheterisation because the definition of this group is still largely subjective.[18]

Along with developments in non-invasive cardiology has grown the inclination to derive new equations that aim to improve assessment by incorporating several variables in much the same way as the Gorlin formula. Such equations are based on the assumption of a precise, usually linear, relation between two or more physiological variables in a patient population. These relations may be applicable to group data, but there is a normal distribution of both physiological variables and their responses to other stimuli that may introduce doubt about applying them to individual patients. Such equations are often an oversimplification of the complex interplay of these physiological and statistical considerations. Bennett's formula which is one such equation[19] assumes that since left ventricular wall stress is directly related to intracavitary pressure the degree of adaptive hypertrophy required to normalise this stress can be used to calculate the left ventricular systolic pressure. On page 155 of this issue Dancy has re-examined Bennett's formula for the estimation of the peak pressure gradient in aortic stenosis and has arrived at two main conclusions.[20] The first obvious but often neglected point is that the quality of the echocardiogram is of paramount importance. In the 42% of Dancy's adult patients who had very high quality echocardiograms the severity of aortic stenosis correlated more strongly with direct measurements of left ventricular wall thickness than with left ventricular mass or pressure derived from Bennett's equation. Echocardiograms of less than this quality were no better than the electrocardiograms in assessing aortic stenosis and their value for predicting the severity of aortic stenosis was not improved by use of the Bennett formula. The second conclusion emphasises the fact that small errors even in the most careful measurements can be magnified several fold if variables are derived from formulas containing complex mathematical functions. A difference of as little as 1 mm in left ventricular dimensions changed calculated left ventricular pressure by 20 mm Hg.

Dancy's work highlights some of the basic dilemmas encountered when mediocre non-invasive data are compared with inaccurate catheter or surgical data. Image quality is relatively easy to define; less definite but probably as important are the skill, care, and experience that among other imponderables constitute the "quality" of non-invasive and catheter data. The weakness of correlative studies that include such data is therefore obvious. These studies often use independent observers to reduce bias but then reintroduce inconsistency in settling differences of opinion by the doubtful concept of consensus. This may provide coefficients of variation which are sound in scientific terms for group data but are probably of little relevance to the clinician and the individual patient. It follows that most of the assumptions about accuracy are illusory. In making decisions the clinician needs to know how much value to place on a particular measurement and therefore it is the 95% confidence limits that are important. A variable with a relatively narrow confidence limit is more useful in distinguishing normal values from abnormal ones and in grading severity of disease than one with wider limits. One way of establishing these limits is to study the reproducibility of these measurements[21 22] and echocardiography is ideal in this respect because it can be repeated many times without risk to the patients. Doppler echocardiography also needs to be studied in this way as it is still in its excellent correlative phase[23 24] and its limitations are yet to be established. The reproducibility of the catheter data against which non-invasive data are compared has been virtually unchallenged because the technique does not lend itself to this approach. Reproducibility studies will need to be performed in each centre and reviewed as experience is gained in using the technique. The emphasis must be on striving for high quality images and poor data should be discarded.

More studies simulating the diagnostic cascade are required to identify the relative merits of these investigations and thus avoid tedious, expensive, and time consuming duplication. Non-invasive techniques can then be used not as a wholesale replacement for cardiac catheterisation but as a substitute in cases where they establish the diagnostic and therapeutic situation beyond doubt.

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*Br Heart J* 1986; 55: 120–8

# Relation between coronary anatomy and serial changes in left ventricular function on exercise: a study using first pass radionuclide angiography with gold-195m

JOHN L CAPLIN, DUNCAN S DYMOND, JAMES C O'KEEFE, WILLIAM D FLATMAN,* LORRAINE DYKE,* SEAMUS O BANIM, ROWORTH A J SPURRELL

*From the Departments of Cardiology and *Nuclear Medicine, St Bartholomew's Hospital, London*

SUMMARY Serial changes in left ventricular function on exercise were assessed by first pass radionuclide angiography with gold-195m (half life 30·5 s) in 25 men with known coronary anatomy. In the seven patients with three vessel disease, abnormalities of global left ventricular function and regional wall motion occurred earlier during exercise, were of greater extent at peak exercise, and persisted longer after exercise than in the 11 patients with one and two vessel disease or the seven with normal coronary arteries. Although there were significant differences between the groups in absolute change in ejection fraction and the rate of change in ejection fraction related to exercise duration and heart rate, a considerable overlap of values between groups precluded the accurate prediction of coronary anatomy in individuals.

These data suggest that the amount of myocardium at risk from ischaemia in some patients with one and two vessel disease may resemble that in patients with three vessel disease. This study shows that an anatomical classification based solely on the number of diseased vessels will not predict the extent of the impairment of left ventricular function on exercise.

Patients with coronary artery disease develop impairment of left ventricular function on exercise, and the extent of this dysfunction can be assessed by radionuclide angiography.[1 2] Peak exercise is necessary to maximise the sensitivity of both the first pass and gated equilibrium techniques.[3 4] It may be, however, that imaging at stages before and after peak exercise could increase the diagnostic precision.

Recent data from exercise electrocardiography have suggested that coronary anatomy can be accurately predicted by assessment of the changes in ST segments related to heart rate (the ST/HR slope) as an index of developing ischaemia.[5] Since radionuclide angiography will estimate the degree of developing ischaemia by the changes in ejection fraction and regional left ventricular wall motion, it might be expected that a functional index derived from these data could predict the extent of coronary disease if such changes were solely related to the number of diseased vessels.

First pass radionuclide angiography can assess rapid changes in left ventricular function, and the development of gold-195m,[6] a radioisotope with an ultra short half life, and its validation for use in man[7] means that multiple rapid sequential studies of left ventricular function are now feasible. This study was designed to assess the time course of changes in left ventricular function during and after exercise and to see how this might be related to the anatomical extent of coronary artery disease.

## Patients and methods

### STUDY POPULATION AND EXCLUSIONS

Twenty five non-consecutive male patients were

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Accepted for publication 19 September 1985

selected on the basis of their coronary anatomy. They had been referred to the cardiac department for assessment of chest pain and had the usual clinical indications for coronary angiography. All were in sinus rhythm, no patient had clinical congestive cardiac failure, and those with an impaired resting ejection fraction (<40%) were excluded. Patients with evidence of previous myocardial infarction were not excluded provided their resting ejection fraction was ≥40%.

### CORONARY ARTERIOGRAPHY

Cardiac catheterisation was performed within two months of the radionuclide study by either the Sones's or Judkins's techniques. The coronary anatomy was assessed by an experienced observer who did not know the result of the radionuclide study. Multiple views of each coronary artery were assessed and the extent of "surgically" important disease (luminal narrowing >50%) in one or more major arteries was noted. On this basis the patients were assigned to groups with *(a)* normal coronaries, *(b)* one and two vessel disease, and *(c)* three vessel disease. No subject in the group with normal coronaries had any obstructive lesions. In addition the coronary anatomy was assessed by means of a weighted coronary index[8] with a score of 1 being normal and a progressive decline to 0 as obstruction increased.

### RADIONUCLIDE ANGIOGRAPHY

All antianginal medications except sublingual nitrates were discontinued for at least 48 hours before the study; beta adrenergic antagonists were discontinued for at least 72 hours before the study.[9 10] Exercise first pass radionuclide angiography was performed in the upright anterior posterior projection with a Baird Atomic System 77 multicrystal gamma camera.[11] An 18 gauge cannula was inserted into a large vein in the antecubital fossa and for each imaging point 15–20 mCi (550–750 MBq) of gold-195m was injected by means of a rapid 20 ml saline solution flush. The portable mercury-195m/gold-195m generator (AERE, Harwell, England) has been described elsewhere.[6] Data were collected for 30 s with 30 ms framing intervals, and they were corrected for instrument dead time, crystal non-uniformity by means of a mercury-203 uniform flood, and rapid decay of the isotope.

Left ventricular ejection fraction was calculated from high frequency time-activity curves by a semiautomated technique. Regional wall motion was derived from count-based regional ejection fraction images.[12] Each image was assessed by an experienced observer who was unaware of the results of the coronary angiogram. The ventricle was visually divided into three equal segments—inferior, apical, and anterior. Regional wall motion was displayed by means of a 16 point colour scale for 100% to 0%, each colour representing 6·25%, and a segment was deemed to be abnormal if at least half of its border had a regional ejection fraction of <50%.[11]

### EXERCISE PROTOCOL

Patients performed maximal graded bicycle exercise in the upright position on an hydraulically braked bicycle ergometer (Fitron). Patients were imaged at rest and then started to cycle at a workload of 400 kpm/minute (67 W) and this was increased by 200 kpm/minute (33 W) every two minutes until peak exercise was reached. Patients were imaged at 3 minutes, at 6 minutes, and then at peak exercise. They were then instructed to continue exercise at as high a workload as possible for a further 2 minutes and they were then imaged as they stopped cycling immediately after exercise. They were then imaged again 2 minutes after exercise. The electrocardiogram (lead II) was monitored throughout the test and pulse rate and cuff arterial pressure were measured at each imaging point.

### RADIATION DOSIMETRY

Subjects who completed the entire study received a maximum of six boluses of gold-195m (approximately 4500 MBq). We have assessed the radiation burden for this level of exposure from the Harwell mercury-195m/gold-195 m generator to be 150 mrem to the kidneys, 17 mrem to the gonads, and 35 mrem to the whole body, based on a mercury-195 breakthrough of <0·01%. The equivalent burden from 1800 MBq of technetium-99 m, as pertechnetate, which would be sufficient for only three studies, is 3500 mrem to the kidneys and 350 mrem to the whole body.

### STATISTICAL METHODS

Statistical analysis was performed by the paired Student's *t* test and Wilcoxon matched pairs signed ranks test to compare changes within a group, and the Mann-Whitney U tests and $\chi^2$ test, as appropriate, for comparisons between groups. A p value of <0·05 was regarded as significant.

## Results

### AGE AND HAEMODYNAMIC VARIABLES AT REST AND ON EXERCISE

Table 1 shows the means (SD) of the ages and haemodynamic variables in each of the groups. The ages of the groups were not significantly different, and the only haemodynamic difference between groups was that peak exercise heart rate was significantly lower in those with three vessel disease than in the

Table 1 *Rest and peak exercise characteristics (mean (SD) ) of the groups*

| | *Age (yr)* | *R HR (bpm)* | *R SBP (mm Hg)* | *R DP ($\times 10^{-2}$)* | *Ex HR (bpm)* | *Ex SBP (mm Hg)* | *Ex DP ($\times 10^{-2}$)* | *Ex Dur (min)* |
|---|---|---|---|---|---|---|---|---|
| Normal coronaries | 49 (10) | 78 (17) | 124 (16) | 96 (20) | 161 (13) | 174 (24) | 282 (56) | 7·2 (1·6) |
| 1+2 vessel disease | 53 (5) | 85 (15) | 144 (33) | 124 (41) | 148 (22) | 187 (38) | 280 (76) | 5·8 (1·1)* |
| 3 vessel disease | 50 (6) | 69 (12) | 137 (21) | 95 (27) | 140 (27)* | 172 (22) | 242 (61) | 5·1 (1·8)* |

*p<0·05 *vs* those with normal arteries
R, rest; Ex, peak exercise, HR, heart rate; SBP, systolic blood pressure; DP, double product of heart rate × blood pressure; Dur, duration.

group with normal coronary arteries (p<0·05). There was, however, no significant difference in the double products or the change in heart rates between the groups. Not surprisingly the main difference between the groups was in the duration of exercise. Patients without important coronary disease were able to exercise for significantly longer than those with coronary disease (p<0·05). Five of the seven with normal coronary arteries but only six of 18 with coronary disease could exercise for 6 minutes or more.

The mean coronary score in the subjects with coronary artery disease was 0·41 (0·20) and ranged from 0·09 to 0·7. The score for the one and two vessel group was 0·48 (0·16) and for the three vessel group it was 0·29 (0·20) (p<0·05).

## SERIAL CHANGES IN EJECTION FRACTION DURING EXERCISE AND AFTER EXERCISE

Figure 1 shows the mean left ventricular ejection fractions in each group at various imaging stages. In those with normal coronary arteries mean ejection fraction was maintained and tended to rise during exercise. Ejection fraction at rest was 60 (3)% (mean (SD)) and rose to 65 (10)% at peak exercise (p, not significant). Two minutes after exercise the ejection fraction (68 (6)%) significantly (p<0·01) exceeded the resting value.

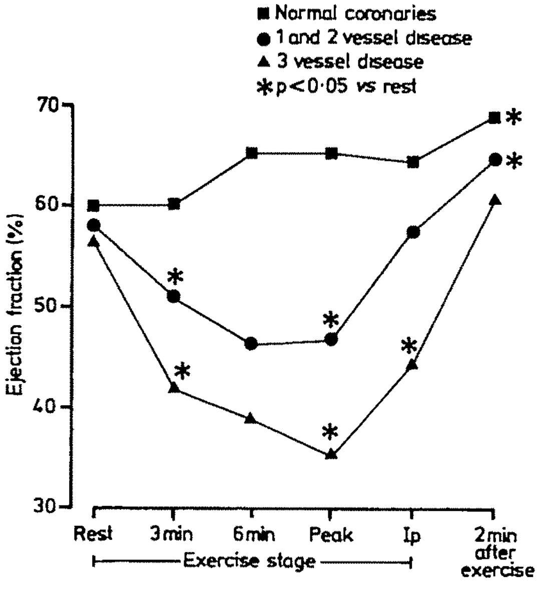

Fig. 1 *Mean ejection fraction of the three groups at each stage. Ip, immediately after exercise.*

In the group with one and two vessel disease the ejection fraction fell during exercise with maximum depression occurring at peak exercise (58 (10)% *vs* 47 (10)%, p<0·01). Mean ejection fraction had returned to the resting level as the patient stopped cycling, immediately after exercise; and by two minutes after exercise the ejection fraction had significantly rebounded above the resting level to 64 (8)% (p<0·05). Nine of the subjects showed this response.

The group with three vessel disease, like those with one and two vessel disease, showed significant falls in ejection fraction on exercise, again with the maximum fall at peak exercise (57 (12)% *vs* 35 (8)%, p<0·001). In contrast with the group with one and two vessel disease the ejection fraction remained depressed immediately after exercise (44 (9)%) (p<0·05 *vs* rest), and there was no significant rebound increase in ejection fraction in this group two minutes after exercise. A typical example of the images in this group is shown in Fig. 2. At any given stage the depression in ejection fraction was greater in the group with three vessel disease than in the group with one and two vessel disease.

Table 2 shows the mean (SD) of the ejection fractions at all the stages in each of the groups. As discussed above there were significant intragroup changes during and after exercise when compared with the resting level. There was no significant difference in the resting ejection fractions between groups. On exercise, however, ejection fraction was significantly depressed in the patients with coronary disease when compared with those without. Immediately after exercise only those with three vessel disease were different from those without coronary disease. Their mean ejection fraction was also significantly lower than that in the group with one and two vessel disease. There was no significant

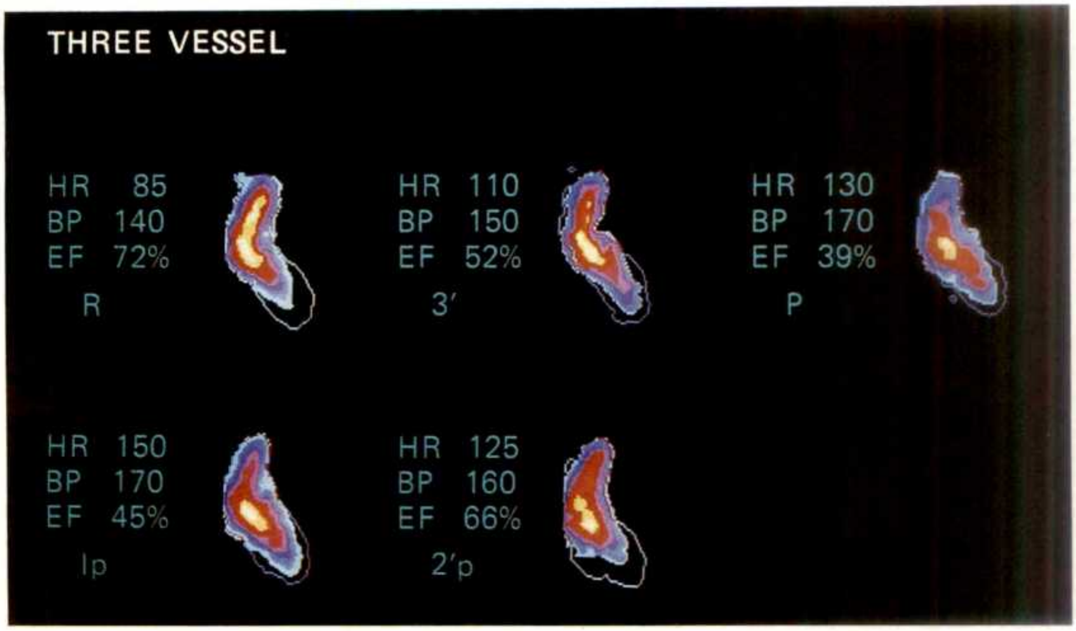

Fig. 2 *Studies in a patient with three vessel disease. The images show the end diastolic perimeter enclosing the end systolic image. HR, heart rate; BP, blood pressure; EF, ejection fraction. R, rest; 3′, 3 minutes exercise; P, peak exercise; Ip, immediately after exercise; 2′p, 2 minutes post-exercise.*

difference between the groups 2 minutes after exercise. At peak exercise patients with three vessel disease also had a significant reduction in ejection fraction compared with those who had one and two vessel disease.

An abnormal ejection fraction response was defined as a fall in ejection fraction of $\geqslant 5\%$ below the value at rest. Table 3 shows the proportion of patients in each group who had an abnormal response. Only one of the patients with normal coronaries had an abnormal response and this was a transient fall of 5%, from 63% to 58% after 3 minutes of exercise. Subsequently his ejection fraction returned to the level at rest. In contrast a large proportion of patients with coronary disease had abnormal responses, and this was related to the extent of the disease. The intergroup difference in proportion of patients with an abnormal response at the various stages is as shown. Patients with one and two vessel disease had a significantly higher proportion of abnormal responses at 6 minutes, at peak exercise, and immediatly after exercise than patients with normal coronaries. In the group with three vessel disease the difference was significant at 3 minutes, peak exercise, and immediately after exercise, suggesting that abnormalities in global left ventricular function tended to occur earlier in this group than in those with one and two vessel disease.

### CHANGES IN REGIONAL WALL MOTION DURING AND AFTER EXERCISE

Table 4 shows the proportion of abnormal segments at each of the imaging stages. At rest one of the seven with normal coronary arteries had a single segmental abnormality, whereas five of the 11 with one and two vessel disease had abnormal segments, and four of seven with three vessel disease had a single segmental abnormality (p not significant).

Table 2 *Ejection fractions (means (SD)) in the groups at various stages of exercise*

| | *Rest* | *Exercise* | | | *After exercise* | |
|---|---|---|---|---|---|---|
| | | *3 min* | *6 min* | *Peak* | *Immediately* | *2 min* |
| Normal coronaries | 60 (3) | 60 (6) | 65 (9) | 65 (10) | 64 (6) | 68 (6)* |
| 1+2 vessel disease | 58 (10) | 51 (10)*† | 46 (12)† | 47 (10)*† | 57 (11) | 64 (8)* |
| 3 vessel disease | 57 (11) | 42 (9)*† | 39 (1)† | 35 (8)*†‡ | 44 (9)*†‡ | 61 (10) |

*$p<0.05$ *vs* rest value (paired *t* test); †$p<0.05$ *vs* normal and ‡$p<0.05$ *vs* 1+2 vessel disease (Mann-Whitney U test).

Table 3 *Proportion of subjects in each group with an abnormal ejection fraction response (fall of ≥ 5%) to exercise at each stage compared with rest*

| *Stage* | *Normal coronaries* | *1 + 2 vessel disease* | *3 vessel disease* |
|---|---|---|---|
| 3 min exercise | 0·14 | 0·45 | 0·71* |
| 6 min exercise | 0·00 | 0·66* | 1·00 |
| Peak exercise | 0·00 | 0·73* | 1·00* |
| Immediately after exercise | 0·00 | 0·45* | 0·71* |
| 2 min after exercise | 0·00 | 0·00 | 0·14 |

At 6 min exercise the result for those with three vessel disease fails to reach statistical significance; however, the number of subjects who reached that stage was small. *$p < 0·05$ *vs* normal coronaries ($\chi^2$ test).

At 3 minutes of exercise the seven with normal coronary arteries had developed a total of six abnormal segments, whereas the 11 with one and two vessel disease had developed 16 segmental abnormalities (p not significant *vs* normal), and the seven with three vessel disease had developed 16 abnormalities ($p < 0·01$ *vs* normal, $p < 0·05$ *vs* one and two vessel disease).

At 6 minutes and at peak exercise segmental abnormalities present early in exercise in those with normal coronary arteries tended to resolve, such that only three segments remained abnormal at peak. In contrast, in the subjects with coronary disease segmental abnormalities invariably became worse during exercise ($p < 0·01$ *vs* normal arteries). In the group with one and two vessel disease there were segmental abnormalities at peak exercise in all but one patient and only one other had less than two abnormal segments. In those with three vessel disease all segments except one were abnormal at peak exercise. Immediately after exercise, despite the return of the mean ejection fraction to control levels in the one and two vessel group, segmental wall motion abnormalities were present in seven of 11 subjects and this result was significant ($p < 0·01$) when compared with the group with normal coronary arteries. All the group with three vessel disease showed persistent wall motion abnormalities immediately after exercise and in three subjects these persisted after 2 minutes' recovery. One of these subjects, who subsequently was found to have a left main stem stenosis in addition to three vessel disease, had persistence of segmental abnormalities in three segments.

In the groups without three vessel disease, there were fewer segmental abnormalities after exercise than before it. This pnenomenon, improvement in resting wall motion abnormalities after exercise, has been reported before.[13]

## RELATION BETWEEN THE DERIVED RATES OF CHANGE IN LEFT VENTRICULAR FUNCTION AND THE EXTENT OF CORONARY DISEASE

Two indices of rates of change in left ventricular function during exercise were derived. The first was a relatively simple measure of total change in ejection fraction from rest to peak exercise divided by the exercise duration—this gave an overall rather than an "instantaneous" rate of change. Figure 3 shows the results of these calculations for each group. The rates were 0·631 (0·982)%/min for those with normal coronary arteries, −2·09 (1·78)%/min for those with one and two vessel disease ($p < 0·01$ *vs* normal), and −4·76 (2·88)%/min for those with three vessel disease ($p < 0·001$ *vs* normal and $p < 0·05$ *vs* one and two vessel disease). Although there were highly significant differences between the groups there is considerable overlap, particularly between

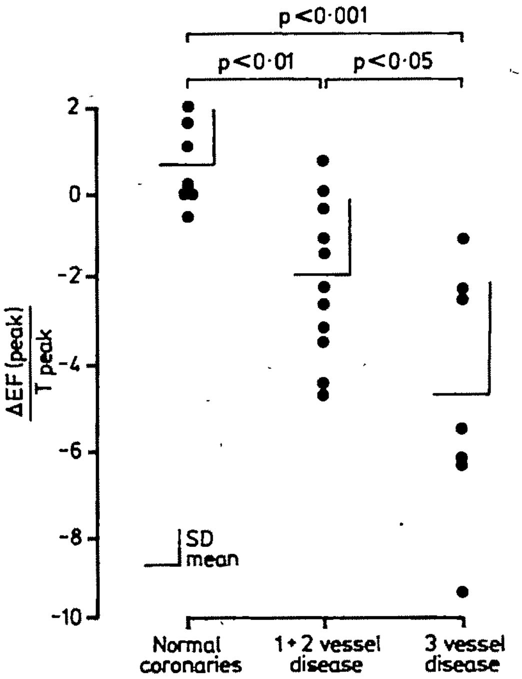

Fig. 3 *Rate of change of ejection fraction to peak exercise (Δ EF(Peak)/T peak) in the three groups. Means, SD, and p values are shown.*

Table 4 *Proportion of abnormal ventricular regional segments at each of the imaging stages in the three groups*

| *Stage* | *Normal coronaries* | *1 + 2 vessel disease* | *3 vessel disease* |
|---|---|---|---|
| Rest | 0·05 | 0·18 | 0·19 |
| 3 min exercise | 0·29 | 0·48 | 0·76*† |
| 6 min exercise | 0·20 | 0·67* | 1·00* |
| Peak exercise | 0·14 | 0·73* | 0·95*† |
| Immediately after exercise | 0·05 | 0·39* | 0·71*† |
| 2 min after exercise | 0·00 | 0·06 | 0·24* |

The left ventricle was divided into three equal segments (inferior, apical, and anterior) and these were deemed to be abnormal if over half of the border had a regional ejection fraction of $<50\%$. $^*p<0\cdot05$ *vs* normal; $^\dagger p<0\cdot05$ *vs* 1 + 2 vessel disease ($\chi^2$ test).

those with normal coronary arteries and those with one and two vessel disease and between those with one and two vessel disease and those with three vessel disease. One of the results in the group with three vessel disease was considerably more negative than the others and this may have biased the mean leading to a spurious significant difference when these results were compared with those in patients with one and two vessel disease.

We examined another index of rate of change of ejection fraction. This was the relation between the rate of change in heart rate derived for each stage of exercise and the maximum negative or minimum positive value noted for each subject. This particular index was chosen because it resembles the ST/HR slope used by some investigators for analysis of exercise electrocardiograms to determine the extent of coronary disease. The rates were 0·0122 (0·0736)%/bpm for those with normal coronary arteries, −0·19 (0·156)%/bpm for those with one and two vessel disease ($p<0\cdot05$ *vs* normal), and −0·407 (0·286)%/bpm for those with three vessel disease ($p<0\cdot01$ *vs* normal and $p<0\cdot05$ *vs* one and two vessel disease) (Fig. 4). As with the first index, although there were significant differences between the groups, the degree of overlap would preclude the use of either algorithm to predict accurately the extent of coronary disease in individuals.

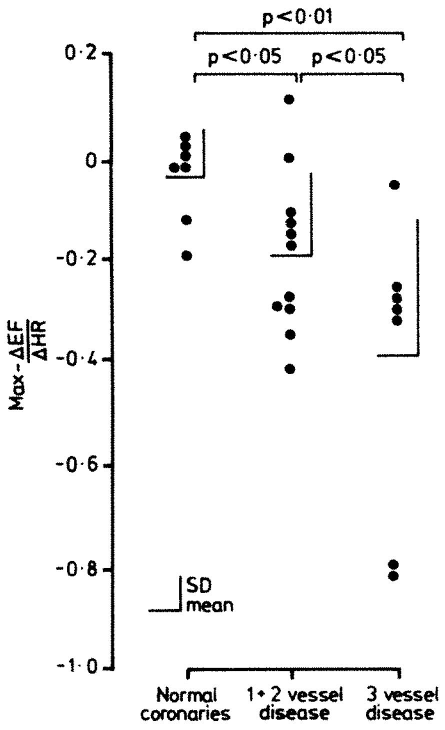

Fig. 4 *Maximum negative (or minimum positive) change of ejection fraction related to change of heart rate (△EF/△HR) in the three groups. Means, SD, and p values are shown.*

Both indices were also compared with the coronary score in those subjects with coronary artery disease. There was no significant correlation between the coronary score and either index. In addition the coronary score was not related to exercise duration or change in ejection fraction. To see whether the coronary score in itself was a better predictor of functional change on exercise we examined the results in two groups—those with a high score of >0·4 (n = 10) and those with a low score of <0·4 (n = 8). There was no significant difference in overall change in ejection fraction at peak exercise in the two groups (−14 (11)% in the high group versus −17 (11)% in the low group). The values for the first index were −2·8 (2·4)%/min for high group and −3·5 (2·9)%/min in the low group (p not significant). For the second index the corresponding figures were −0·26 (0·24)%/bpm and −0·29 (0·24)%/bpm respectively (p not significant).

## Discussion

Radionuclide angiography is an accepted method for the assessment of patients with chest pain and suspected coronary artery disease.[1 2] Although coronary angiography is the universally accepted standard by which non-invasive techniques are judged, it has its limitations. First it is an invasive technique that may cause morbidity and mortality,[14] and seondly it provides information about anatomy rather than function.

Exercise testing in patients with coronary disease produces impairment of left ventricular function which reflects the extent of ischaemia. Therefore non-invasive methods that can quantity changes in left ventricular function provide information on the magnitude and rate of development of ischaemia.

It is possible to study left ventricular function at various stages of exercise by means of equilibrium gated radionuclide angiography, but the time required for data acquisition, two minutes at least, will blur any rapid changes. First pass studies, in which transit of radioisotope through the left heart lasts for only a few seconds, can be used to assess rapid changes in left ventricular function, but an injection of radioisotope is required at each imaging point. Thus radiation exposure constrains the number of injections to a maximum of three per study of conventional technetium-99m based radiopharmaceuticals. The development of radiopharmaceuticals with ultrashort half lifes[6] has meant that not only the extent, but also the time course of changes in function on exercise may be studied. If the magnitude or rate of development of functional impairment were directly related to the coronary anatomy it might be possible to predict the extent of coronary disease by examining the time course of these changes.

In this study a group of patients who had a clinical indication for coronary angiography and relatively preserved resting left ventricular function were studied by multiple rapid sequential first pass radionuclide angiography with gold-195m. There were no significant differences in terms of age, resting ejection fraction, and resting and exercise haemodynamics between patients with normal coronary arteries and those with mild or severe coronary disease. Subjects with normal coronary arteries exercised for significantly longer than those with coronary disease, and they tended to maintain or increase their ejection fraction throughout exercise, with a significant rebound of ejection fraction above the level at rest after exercise. This rebound has been previously documented both after bicycle[3 15] and treadmill exercise,[16] and is thought to be due to sudden reductions in afterload and heart rate on cessation of exercise coupled with a maintained metabolic requirement that leads to an increase in stroke volume and hence ejection fraction.[3]

In patients with one and two vessel disease there was a significant fall in ejection fraction on exercise with the maximum fall being at peak exercise. In this group there was a rapid return of ejection fraction to the resting level immediately after exercise and a rebound above the rest level at two minutes.

In the group with three vessel disease, ejection fraction fell throughout exercise. Again the fall was maximal at peak exercise. In this group the fall in ejection fraction was greater at each stage than in those with one and two vessel disease. These patients still showed abnormalities after exercise and some of the group were abnormal even after two minutes of recovery.

These data suggested that patients with varying degrees of coronary obstruction could be distinguished by their ejection fraction response to exercise, but there was some overlap between the groups. The rebound in ejection fraction during recovery noted above seems unrelated to the type of exercise since it has been reported for supine[15] and upright bicycle exercise[3] and treadmill exercise.[16] Furthermore, lack of rebound seems to be associated with an increased likelihood of ischaemic pain during exercise and, as confirmed by this study, more extensive coronary disease.

Further assessment of regional wall motion also showed significant differences between the groups. Subjects with three vessel disease tended to develop segmental abnormalities early and these persisted longer after exercise than in the other groups. Again despite these significant differences the overlap in results in the individual subjects precludes definite anatomical diagnosis.

These data suggested that subjects with more extensive coronary artery disease had a greater likelihood of developing changes in global ejection fraction or regional wall motion early in exercise than subjects with less severe disease. This complements a previous study of exercise electrocardiography in which a positive test occurring early during exercise has been shown to be associated with more extensive coronary artery disease and a worse outcome.[17] Thus the rate of change in ejection fraction might allow better discrimination of the extent of coronary disease than the overall change in ejection fraction at peak exercise. Because of this we also assessed two indices of the rate of change in ejection fraction. In the first a measure of the overall rate of change of ejection fraction was derived. This showed that there were significant differences between the groups but that there was considerable overlap of individual values.

The second index related the maximum fall in ejection fraction to changes in heart rate. This was chosen to be analogous to the exercise electrocardiographic ST/HR slope that has been reported to predict coronary anatomy by some workers[5] but not others.[18] Although there were significant differences between the groups, again there was a considerable overlap of values. The relation between these indices and a widely used coronary score[8] again failed to predict the extent of coronary disease.

The data from both these indices (Figs. 3 and 4) show that there is a general relation between the extent of coronary artery obstruction and the degree of functional impairment on exercise. The extent of overlap between those with severe and less severe coronary artery disease is not surprising. If the degree of ischaemia were related solely to the number of diseased vessels, ignoring the vessel dominance, number, site, severity and length of the lesions, and the presence of collaterals, this would be an example of almost unique biological homogeneity.[19]

The first index, which relates change in ejection fraction to exercise duration, may be suitable for use in studies in which gold-195m is not available. It may be that further studies will extend the accuracy of this index by generation of an algorithm relating it to the anatomical extent of coronary disease. The second index, which is based on heart rate change, may also be adapted to conventional studies, and it might be of use when the heart rate response is attenuated as it is in subjects who are unable to exercise maximally. Both indices may also be of use in the more accurate assessment of myocardium in jeopardy from ischaemia. Indeed outcome in patients with coronary artery disease is more closely related to an index of coronary artery jeopardy, and hence myocardium at risk, than to the number of diseased vessels.[20]

The failure of any of these direct or derived indices of changing left ventricular function on exercise to predict accurately the number of diseased coronary vessels suggests a discrepancy between functional and anatomical assessments of the extent of ischaemic heart disease. Because changes in ejection fraction on exercise are affected not only by the development of ischaemia but also by changes in preload and afterload there are reservations about the usefulness in the diagnosis of coronary disease of a single measure of left ventricular ejection fraction during exercise. None the less an assessment of the amount of myocardium at risk remains the single most prognostically useful measurement in these patients.[21]

Prognosis in patients with three vessel disease can be altered by coronary artery bypass surgery,[22] and indeed the present study has shown that as a group these patients do have more myocardium at risk from ischaemia. In some patients with three vessel disease, however, left ventricular function on exercise is preserved, and in such patients the prognosis without surgery is good.[21] It may be that those who have less than three vessel disease but who have functional impairment similar to those with three vessel disease are at higher risk and would therefore benefit from revascularisation. This hypothesis requires further study. Data to support this have come from a long term prospective trial of coronary artery surgery which suggested that the long term outcome in some patients with two vessel disease is similar to that in patients with three vessel disease.[23] If this is subsequently confirmed then the non-invasive assessment of left ventricular function at rest and exercise may, in the future, be as important as coronary anatomy in the selection of patients who will benefit from coronary surgery.

Dr Caplin is supported by the British Heart Foundation.

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# Potential errors in the estimation of coronary arterial stenosis from clinical arteriography with reference to the shape of the coronary arterial lumen

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SUMMARY Underestimation of coronary arterial stenosis at clinical arteriography has been explained by inadequate radiological views of crescentic or slit-shaped lumens. Postmortem perfusion-fixation of the coronary arteries at physiological pressures shows that most stenotic lesions result in circular, elliptical, or D-shaped lumens. Crescentic lumens in fully distended vessels are associated only with acute mural thrombus projecting into the lumen or with massive intra-intimal thrombus and plaque fissuring. Elliptical and D-shaped lumens, however, adequately explain the clinically observed phenomenon that some stenotic lesions can be seen only in one $x$-ray plane and not in another. It is no longer correct to postulate a crescentic or slit-like lumen. Furthermore, not only can elliptical and D-shaped lumens result in underestimation of stenosis, they may also result in serious overestimation. Lumens need only to deviate slightly from being circular for error to be introduced into the estimation of stenosis by currently used methods. The calculation of percentage stenosis from densitometric measurements or from computerised reconstruction of the arterial lumen is, however, more accurate.

The estimation of coronary arterial stenosis from clinical arteriography is usually made by comparing the diameter of the coronary lumen at the point of stenosis with that of an adjacent presumably normal arterial segment in the radio-opaque contrast filled artery (percentage stenosis by diameter). It is widely accepted that such measurements may underestimate the degree of arterial stenosis if one plane only is available for examination. The usual explanation given is that the residual coronary arterial lumen is slit-like or crescentic in shape.[1] [2] These explanations derive from widespread illustration of irregularly shaped lumens in standard textbooks and from the common belief that atheromatous plaques bulge into the lumen. Histological sections depicting such irregular shapes are, however, obtained from material that has been

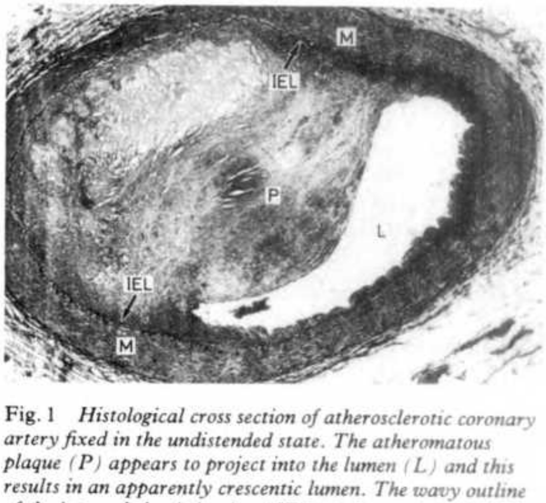

Fig. 1 *Histological cross section of atherosclerotic coronary artery fixed in the undistended state. The atheromatous plaque (P) appears to project into the lumen (L) and this results in an apparently crescentic lumen. The wavy outline of the internal elastic lamina (IEL) indicates fixation in the undistended state. M, media. Elastic haematoxylin and eosin × 45 (original magnification).*

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Accepted for publication 1 October 1985

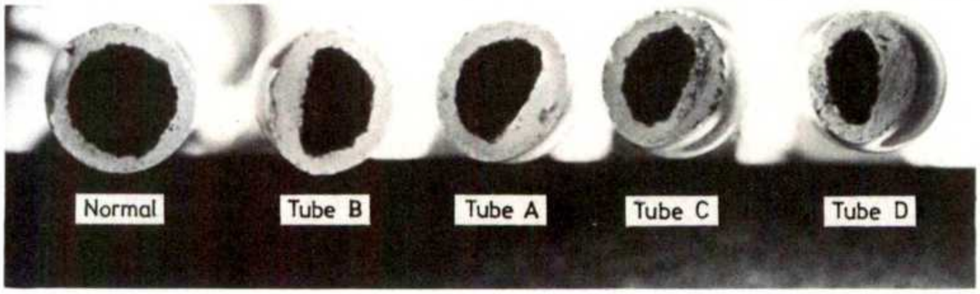


Fig. 2 *Cross sections of four manipulated glass tubes (A to D) transected at maximum points of stenoses to show residual ovoid lumens compared with cross section of normal unmanipulated glass tube with circular lumen.*

fixed and processed in the undistended state (Fig. 1). Crawford and Levene in 1953 showed that the "raised fibrofatty plaque" was somewhat of a misnomer and that though atheromatous plaques in arteries fixed in complete distension reduced luminal cross sectional area they did not project into the arterial lumen as a hump with well defined margins but appeared en face as changes in consistency and colour.[3] Other workers later confirmed this finding and concluded that most diseased arterial segments had circular lumens and that crescentic lumens were rarely seen.[4-7] Percentage stenosis in histological sections is usually calculated from vessel and lumen perimeters assuming these to be circumferences of circles in calculating cross sectional area. This method overcomes any distortion introduced by undistended vessels and in the production of a histological section but might introduce important errors if indeed the lumens are not circular.

The objects of the present study were to investigate the shape of the diseased coronary artery lumen, to prove conclusively whether or not crescentic and slit-like lumens occur in fully distended diseased coronary arterial segments, to observe the effects of luminal shape on estimation of coronary artery stenosis, and to explore alternative more accurate methods for such estimation.

## Materials and methods

### DETERMINATION OF THE CORONARY ARTERIAL LUMEN SHAPE

The hearts of nine patients who died of ischaemic heart disease were perfused-fixed at either 100 or 150 mm Hg with 10% formol saline by tying a large cannula into the aortic root. Under pressure the normal aortic valve closes and the coronary arteries are perfused-fixed in the fully distended state.[8] After perfusion-fixation for 24–48 hours, postmortem angiography was carried out by injecting a warm suspension of 5% gelatin/barium sulphate at a pressure corresponding to the perfusion-fixation pressure and allowing this to solidify within the coronary lumen. This technique allowed localisation of stenotic lesions by *x*-ray examination and supported the arterial wall during the subsequent processing to produce histological sections, a process which may cause considerable distortion of lumen shapes in undistended vessels. In each heart the epicardial coronary arterial tree was dissected en bloc with surrounding adipose tissue and decalcified for 72 hours in 10% formic acid. After decalcification the coronary arteries were transversely sectioned every 3 mm throughout their lengths; we ensured that the transverse sections were perpendicular to the longitudinal axis of the artery. Selected segments were examined and

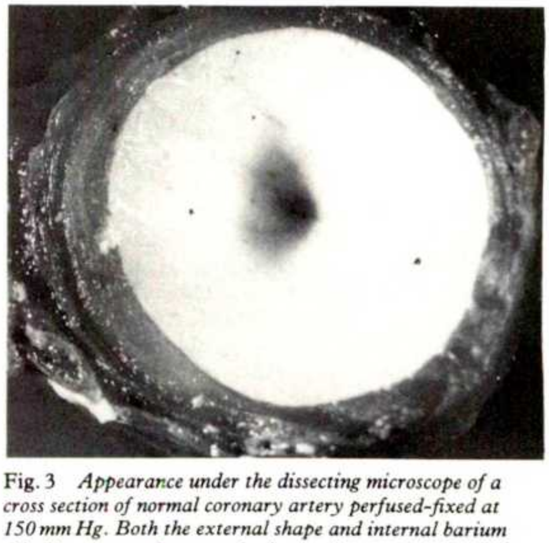


Fig. 3 *Appearance under the dissecting microscope of a cross section of normal coronary artery perfused-fixed at 150 mm Hg. Both the external shape and internal barium filled lumen are almost perfectly circular.* × 25 *(original magnification).*

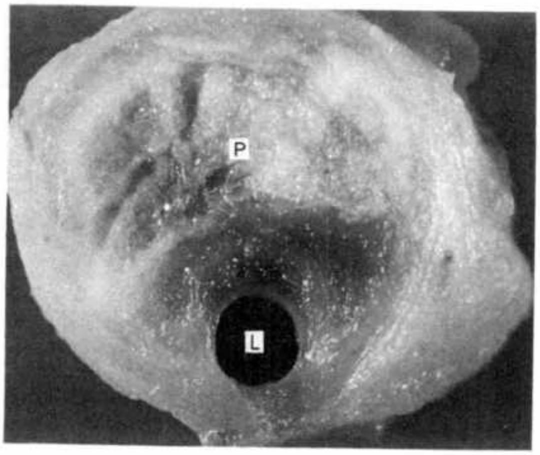


Fig. 4 *Appearance under dissecting microscope of cross section of atherosclerotic coronary artery perfused-fixed at 150 mm Hg. The residual lumen (L) approximates to being a circle although it is eccentrically positioned. P, atheromatous plaque. × 25 (original magnification).*

photographed (without further preparation) under the dissecting microscope. Histological sections of each paraffin embedded 3 mm segment were prepared, stained with an elastic haematoxylin and eosin technique, examined under the light microscope, and compared with the corresponding gross appearance under the dissecting microscope.

### INVESTIGATION OF EFFECT OF LUMEN SHAPE ON OBSERVED PERCENTAGE STENOSIS

#### *Computer simulation*

A BBC Model B microcomputer (Acorn Co.) was programmed to construct a simulation of a cross section of coronary artery in which the vessel outline is circular but the stenosed lumen may be chosen as a circle, ellipse, or D shape and where the D shape may be formed of two half ellipses. (The term "ovoid" is used to include ellipses and all D shapes.) The program allows a full range of choice of the position of the centre of the lumen, vertical and horizontal diameters, and $x$-ray beam incidence. It then offers a print out of ($a$) the observed percentage stenosis by diameter; ($b$) the observed percentage stenosis by cross sectional area, assuming the observed lumen and vessel widths are diameters of circles; and ($c$) the true percentage stenosis by cross sectional area. The program can then produce graphs of the observed percentage stenosis as diameter or cross sectional area measurements against degrees of rotation of the incident $x$-ray beam. A similar graph of lumen position and observed lumen width against degrees of $x$-ray rotation can also be obtained. Finally, for any given $x$-ray beam incidence the program will plot a densitometric readout of the vessel lumen. From the shapes and positions of such densitometric readouts in various $x$-ray planes predictions about the size and shape of the actual lumen may be made.

#### *Experimental study*

Artificial stenoses of varying severity were created in glass tubes by manipulating the heated glass to give residual ovoid lumens (Fig. 2). The glass tubes were filled with a 5% gelatin/barium sulphate suspension and radiographs were subsequently obtained through different degrees of rotation in the horizontal plane when the $x$-ray beam was perpendicular to the long axis of the tubes. The tubes were rotated through varying degrees in the vertical plane when the $x$-ray beam was no longer perpendicular to the long axis of the tubes, and this was also performed for different degrees of rotation in the horizontal plane. The observed percentage stenoses by diameter and corresponding cross sectional area, assuming the observed lumen and vessel widths to be diameters of circles, were calculated for each position. The true percentage stenosis of the cross sectional area was measured by planimetry from cross sections of the glass tubes.

## Results

#### *Determination of coronary arterial lumen shape*

Normal arterial segments which have been perfused-fixed in the fully distended state at physiological pressures have both a circular external shape and a circular lumen when viewed at right angles to the arterial longitudinal axis (Fig. 3). The corresponding histological sections show the internal elastic lamina to be smoothed out, indicating that the artery has indeed been fixed in a state analogous to full dilatation in life. Any deviation from a circular lumen seen in histological sections is a result of distortion at the time of preparing the sections and is a purely technical artefact. Cross sections that are not made perpendicular to the longitudinal arterial axis will result in ovoid shaped lumens when they are viewed end on at right angles to the plane of cut. The external shape of the artery, however, will also be ovoid.

In atherosclerotic arterial segments most of the lumens approximated to being circular but are often placed eccentrically to the midline of the vessel (Fig. 4). Elliptical and D-shaped lumens are seen in diseased segments viewed perpendicularly to the longitudinal arterial axis in hearts perfused-fixed at 100 mm Hg and 150 mm Hg (Figs. 5a, b, and c).

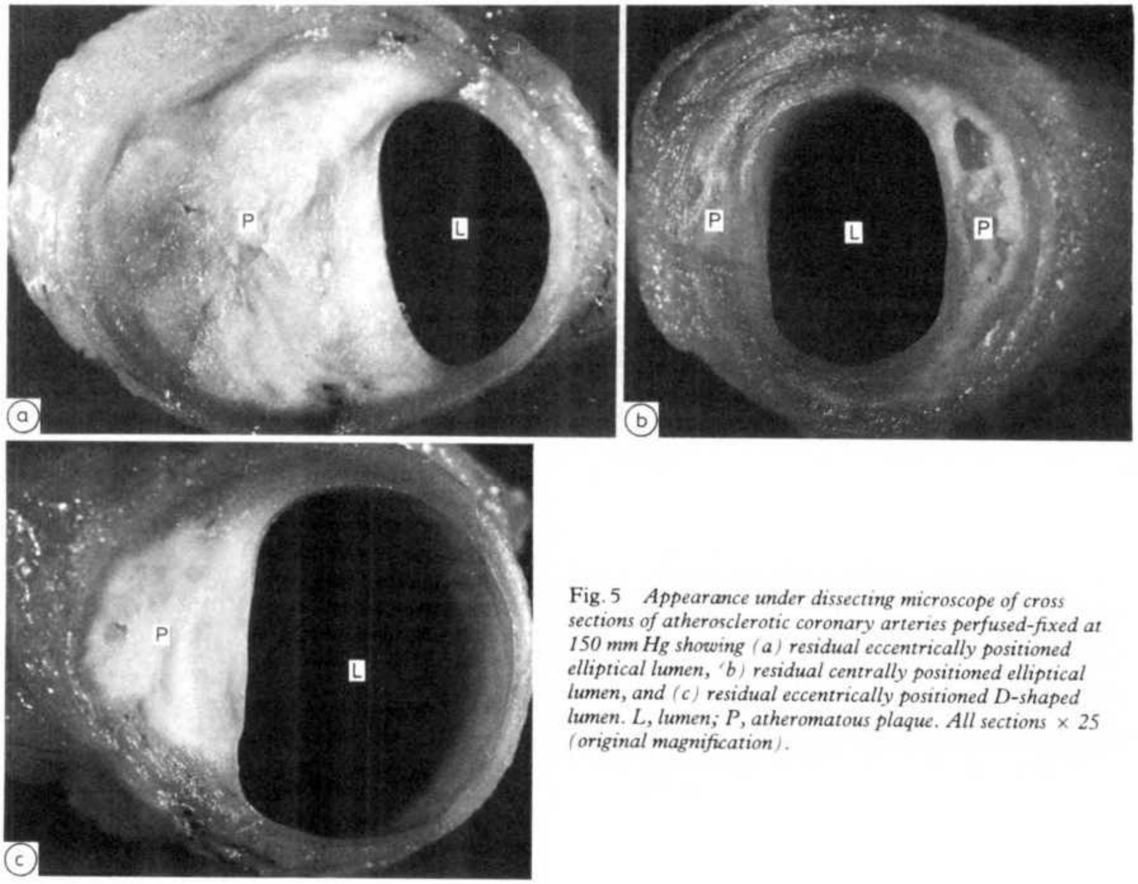


Fig. 5 *Appearance under dissecting microscope of cross sections of atherosclerotic coronary arteries perfused-fixed at 150 mm Hg showing (a) residual eccentrically positioned elliptical lumen, (b) residual centrally positioned elliptical lumen, and (c) residual eccentrically positioned D-shaped lumen. L, lumen; P, atheromatous plaque. All sections × 25 (original magnification).*

The external shape of the artery is often ovoid as a result of the atheromatous plaque bulging outward into the media and is often associated with focal destruction of the internal elastic lamina. The corresponding histological sections confirm complete distension as judged by a smooth internal elastic lamina where present (Fig. 6). The lumen appears to be flattened over the fibrous cap of a plaque, which is often associated with an underlying lipid-rich pool. Not all lipid-rich plaques give rise to elliptical or D-shaped lumens; some are associated with circular lumens. Most hard fibrous plaques without lipid-rich pools, however, result in circular lumens. Slit-like and crescentic lumens do occur, but only with rapidly evolving lesions in which blood from the lumen has tracked into the atheromatous plaque via a fissure and this has led to massive intra-intimal thrombosis or in which a polypoidal mass of thrombus projects into the lumen (Figs. 7a and b). Crescentic and slit-like lumens are not a feature of atheromatous plaques uncomplicated by acute thrombosis and plaque fissuring.

## INVESTIGATION OF EFFECT OF LUMEN SHAPE ON OBSERVED PERCENTAGE STENOSIS

### *Computer simulation*

The computer program shows that for a coronary artery lumen that is circular there is no variation in the observed degree of stenosis for different rotational $x$-ray planes, though the observed position of the stenosis will change if the lumen is eccentrically placed within the vessel.

Ovoid lumens, which are known to occur in fully distended atherosclerotic arteries, show considerable variation in the degree of observed stenosis depending upon the rotational $x$-ray plane. Calculation by area of the observed stenosis can both overestimate and underestimate the true stenosis (Fig. 8), but underestimation will occur by a greater amount and for a wider range of incident $x$-ray beam angles. This is because an elliptical lumen with

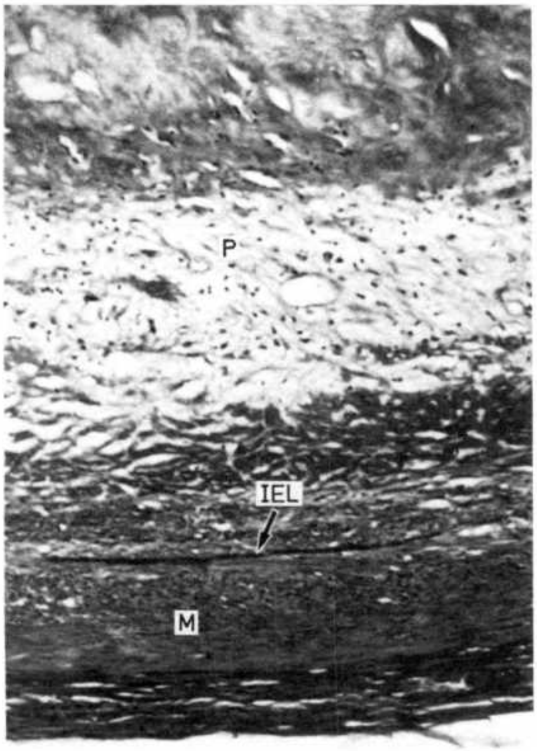


Fig. 6 *Histological section of atherosclerotic coronary artery perfused-fixed in full distension as shown by smooth internal elastic lamina (IEL) (see Fig. 1). P, atheromatous plaque; M, media. Elastic haematoxylin and eosin × 180 (original magnification).*

principal radii A and B will have a true area of $\pi AB$ whereas the calculated circular area will range from $\pi A^2$ to $\pi B^2$. The correct area will be calculated when the measured radius (M) equals $\sqrt{AB}$ and, hence, $\pi M^2 = \pi AB$. The square root of $A \times B$ will always be closer to the smaller radius and so luminal area will be more severely overestimated, thus producing a greater error in underestimating percentage stenosis.

Varying the principal radii while maintaining a constant area influences both maximum overestimates and underestimates and also the range of incident $x$-ray beam angles for which over and under estimates will occur (Fig. 8b).

For luminal shapes with the same maximum and minimum diameters the range of incident $x$-ray beam angles for which the observed stenosis is underestimated also depends on the shape of the lumen (Fig. 8c). The graph of calculated stenosis area against beam angle gives an approximate sine wave for an ellipse but not for a D shape. Therefore, although a D-shaped lumen will result in a maximum under and over estimate of stenosis identical to that of an ellipse, a greater percentage of beam angles will result in an underestimate than with the elliptical lumen.

For any given $x$-ray beam incidence the area covered by the densitometric luminal readout will reflect exactly the true luminal cross sectional area irrespective of the shape of the lumen. If this can be related to a similar densitometric readout of a normal segment of artery, then densitometry will provide a true percentage measurement of cross sectional area stenosis (Fig. 9). In order to predict

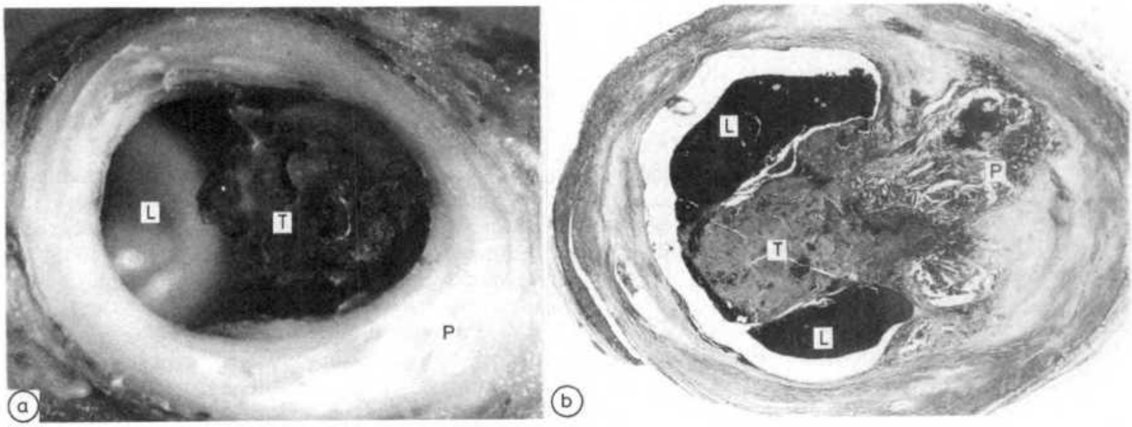


Fig. 7 *Cross section of atherosclerotic coronary artery perfused-fixed at 150 mm Hg showing residual partly barium filled crescentic lumen (L) produced by projection of polypoidal mass of acute thrombus (T) into arterial lumen. P, atheromatous plaque. (a) Appearance under dissecting microscope (× 25 (original magnification)). (b) Corresponding histology and appearance under light microscope (× 30 (original magnification)).*

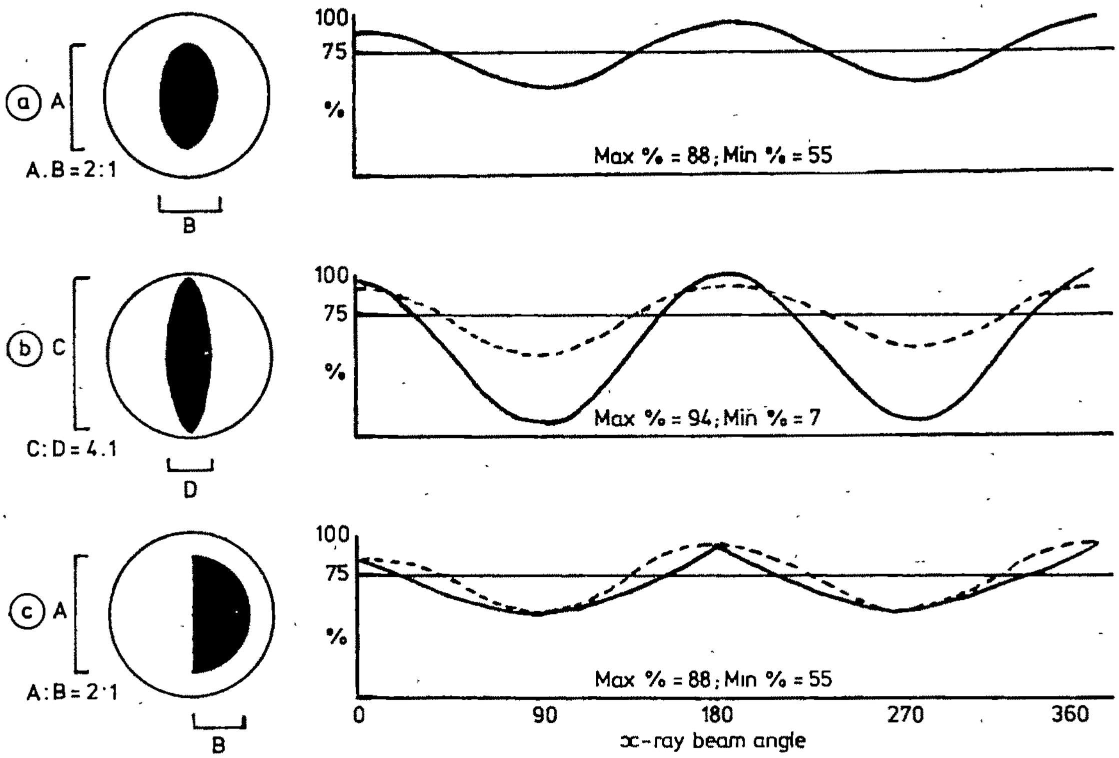


Fig. 8 *Graphs in which calculated stenosis area is plotted against x-ray beam angle. Each of the lumens has a true stenosis area of 75% of the maximum vessel area as indicated by the horizontal line on the graph. (a) The ratio of the principal diameters (and therefore radii). A:B is 2:1 of the central elliptical lumen. (b) The ratio C:D is now 4:1. This greatly increases the maximum and minimum estimation error and also increases the range of beam angles at which stenosis is underestimated. (c) The principal diameters A and B are the same as for (a). This illustrates the effect of lumen shape on the range of beam angles at which stenosis is underestimated. Dotted line in b and c indicates superimposed graph from (a).*

the shape and position of the arterial lumen, however, different densitometric readouts of the same stenotic lumen at different known angles of rotation are necessary. Limiting the possible stenotic luminal shapes to those found at necropsy reduces the number of $x$-ray studies required for reconstruction.

*Experimental study*

The results of the computer simulations were confirmed experimentally by means of the barium filled glass tubes with artificially created stenoses.

Figure 10 shows the effect of observed stenosis of rotating a residual ovoid shaped lumen through varying degrees in the horizontal plane. The observed cross sectional area of stenosis may vary between 36% and 82% (equivalent to 20% and 58% by diameter) for a true fixed cross sectional area stenosis of 58%.

If the incident $x$-ray beam is not perpendicular to the longitudinal axis of the barium filled lumen (that is differing degrees of vertical rotation) the degree of stenosis will be further underestimated (Fig. 11). This underestimation will only be pronounced when the incident $x$-ray beam forms an angle of 45° or less with the longitudinal axis of the vessel, is seen mainly with the more severe stenoses, and is a consequence of an adjacent normal segment being superimposed on the stenotic segment.

## Discussion

During the investigation of coronary artery disease by postmortem angiography we became aware that

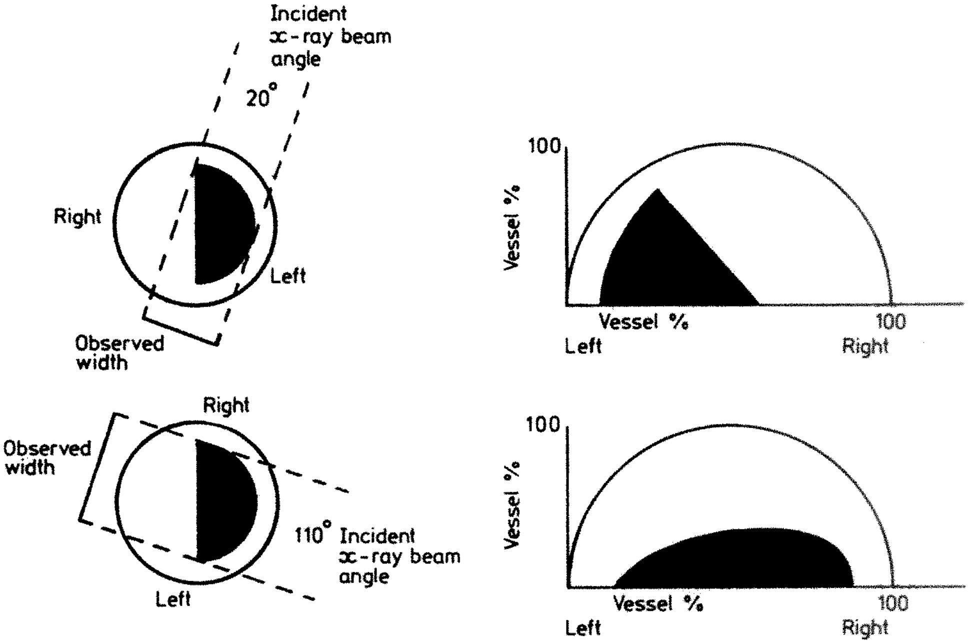
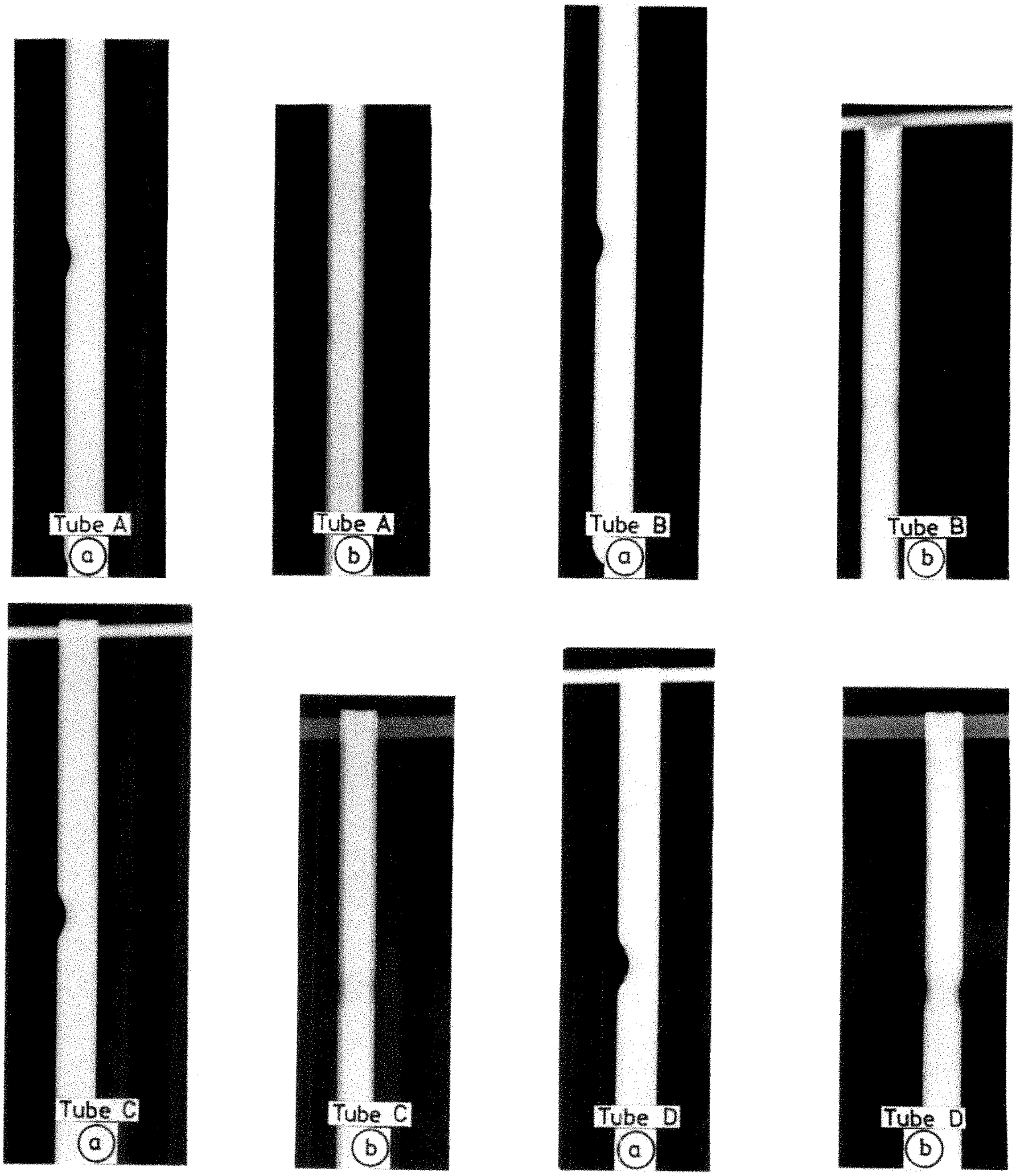


Fig. 9 *Densitometric readings for a D-shaped lumen with a true stenosis area of 75% at beam angles of 20° and 110°. The solid black areas represent the stenosed lumen and corresponding densitometric recording. The area within the continuous line represents the maximum recording for non-stenosed vessel. The densitometric scan proceeds in the direction of the x-ray beam from left to right. Whatever the lumen shape or x-ray beam angles comparison of the stenosed and non-stenosed regions will give a true percentage stenosis area.*

slit-like and crescentic shaped lumens were rare. In our previous studies postmortem coronary angiography was carried out by injection of a warm suspension of 5% gelatin/barium sulphate into the coronary ostia of the fresh intact heart at a monitored pressure of 100 mm Hg and ligation of the coronary arteries on withdrawal of the cannula.[9] The gelatin/barium suspension set solid within the epicardial coronary arterial tree and the heart was fixed intact in 10% formol saline so that the arteries were fixed in distension. Subsequent histological sections of these barium filled coronary arteries after decalcification showed that the residual lumen in diseased segments approximated to being circular, although it was often eccentrically placed, and that crescentic shaped lumens were only encountered in association with plaque fissuring and thrombosis. These observations were in general agreement with those of Freudenberg and Lichtlen who, using a similar technique for postmortem angiography, found that 74% of all significantly stenosed vessels had eccentric lumens and 26% central lumens.[10] Ninety five per cent of all lumens in their cases approximated to being circular, elliptical, or D-shaped while only 5% showed irregular star-shaped or crescentic lumens. With postmortem angiography alone and use of a viscous injection medium, however, it is difficult to ensure complete distension of vessels even when the monitored injection pressure is as high as 150 mm Hg. Certainly a vessel beyond a severe stenosis may be filled at a much lower pressure than that actually monitored and this might account for a few examples of irregular star-shaped lumens observed by Freudenberg and Lichtlen. Furthermore, even in non-diseased arteries that were fully distended (as judged by the histological appearance of a smoothed out internal elastic lamina) the lumen was sometimes distorted as a result of technical problems encountered in the production of a histological section.

The present study ensured fixation of arterial lumens in complete distension by perfusion-fixation of the intact coronary arteries at a constant and monitored perfusion pressure of either 100 or 150 mm Hg with low viscosity formol saline. Examination of cross sections of coronary arterial segments with the dissecting microscope before

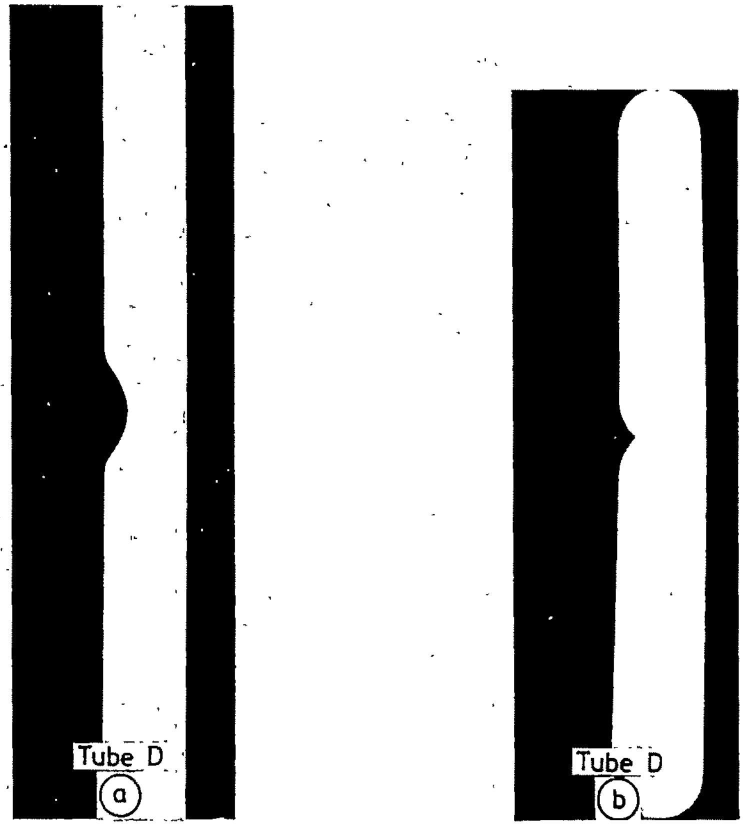
Fig. 10 *Radiographs of barium filled glass tubes (A to D) with artificially created stenoses of varying severity and resultant elliptical lumens (see Fig. 2). Percentage stenoses by diameter and corresponding cross sectional area at maximum point of constriction were calculated from diameters observed through varying degrees of horizontal rotation and compared with true cross sectional area stenosis measured by planimetry. x-ray beam 90° to longitudinal axis of tubes. (a) Optimum rotational plane to give maximum observed stenosis. (b) Rotational plane 90° to optimum plane.*



| *Degrees rotation* | *Tube A (% stenosis)* | | *Tube B (% stenosis)* | | *Tube C (% stenosis)* | | *Tube D (% stenosis)* | |
|---|---|---|---|---|---|---|---|---|
| | *D* | *A* | *D* | *A* | *D* | *A* | *D* | *A* |
| 0 | 20 | 36 | 30 | 51 | 36 | 59 | 56 | 81 |
| 20 | 30 | 51 | 36 | 59 | 46 | 71 | 58 | 82 |
| 40 | 30 | 51 | 28 | 48 | 40 | 64 | 50 | 75 |
| 60 | 18 | 33 | 20 | 36 | 28 | 48 | 38 | 62 |
| 80 | 10 | 19 | 10 | 19 | 16 | 29 | 24 | 42 |
| 100 | 2 | 4 | 0 | 0 | 4 | 8 | 20 | 36 |
| True stenosis area (%) | | 32 | | 36 | | 41 | | 58 |

D, diameter; A, area.

Fig. 1 *Radiographs of barium filled glass tube D in optimum horizontal plane to give maximum observed stenosis. (a) Incident x ray beam 90° to longitudinal axis of tube (0° vertical rotation). (b) Incident x ray beam 30° to longitudinal axis of tube (60° vertical rotation)). Percentage stenoses by diameter and corresponding cross sectional area at maximum point of constriction were calculated from observed diameters for two horizontal planes through varying degrees of vertical rotation and were compared with true cross sectional area stenosis as measured by planimetry for tube D.*



| *Vertical rotation* | *Optimum horizontal rotational plane to give maximum observed stenosis (% stenosis)* | | *Horizontal rotational plane 90° to optimum plane (% stenosis)* | |
|---|---|---|---|---|
| | *Diameter* | *Area* | *Diameter* | *Area* |
| 0° | 58 | 82 | 20 | 36 |
| 20° | 54 | 79 | 19 | 35 |
| 40° | 53 | 78 | 19 | 34 |
| 60° | 13 | 24 | 18 | 33 |
| True stenosis area (%) | — | 58 | — | 58 |

histological processing and light microscopy corrected any problem of luminal distortion which occurred for purely technical reasons. It is essential to decalcify the epicardial coronary arterial tree before transverse sectioning. Failure to do this may well result in gross distortion of the lumen in calcified arteries, the whole vessel wall effectively being crushed rather than sectioned.

By using perfusion-fixation, decalcification, and examination of transverse arterial segments with the dissecting microscope, we obtained results that accorded with those of Freudenberg and Lichtlen—that is although the lumens associated with uncomplicated atheromatous plaques were approximately circular most were elliptical or D-shaped and often eccentrically placed. We were able to confirm our suspicion that slit-like and crescentic shaped lumens were rare. Subsequent histological examination with the light microscope confirmed that such shapes indicated a polypoidal mass of acute mural thrombus which projected into the arterial lumen or massive intra-intimal thrombus formation which had occurred as a result of blood tracking into the intimal plaque via a fissure.

If crescentic and slit-like lumens are not a feature of uncomplicated atheromatous plaques, one must question whether small deviations from a circular lumen (elliptical or D shapes) are sufficient to explain underestimation of coronary arterial stenosis from clinical arteriography. Both the computer simulation study and the experimental work with barium filled glass tubes in which stenoses were artificially created show conclusively that single plane views of ovoid lumens not only give underestimates of the degree of stenosis but may also give gross overestimates of stenosis. The greatest discrepancies occur with ovoid lumens where the ratio of the two principal radii is highest. Underestimates will occur for a wider range of *x*-ray beam angles than overestimates and this range of beam angles is affected by both the ratio of the principal radii and the lumen shape. It is no longer correct to implicate a crescentic shaped lumen to explain the observed discrepancies. It has been suggested, however, that since most residual lumens in diseased coronary arterial segments are eccentric there must be a portion of relatively normal arterial wall capable of responding to vasoconstrictive agents during life, although much of the arterial wall will be fixed and incapable of any response.[11 12] This feature may result in an asymmetrical response to vasoconstriction and accentuate the appearance of any elliptical or D-shaped lumen. Whether a slit-like lumen can result is as yet unknown. Furthermore it is debatable whether a diseased vessel with a centrally placed residual lumen is capable of vasoconstriction. The potential dynamics of such luminal shapes are well reviewed by Brown *et al.*[11 12]

As regards interpretation of clinical arteriography in terms of the degree of arterial stenosis, the fact remains that errors will occur if only one plane of view is examined. Even if views in two planes are available the maximum stenosis observed is the usually accepted value but this in fact might represent an overestimation of the degree of stenosis. It is extremely difficult if not impossible to obtain more than one meaningful view of certain areas of the coronary artery anatomy. The problems are compounded when the incident *x*-ray beam is not perpendicular to the longitudinal axis of the vessel. Given that many residual lumens are non-circular, it follows that to report these in terms of percentage stenosis by diameter may be just as misleading. Equally, calculation of percentage stenosis by cross sectional area derived from diameters on the assumption that the lumen is circular may be just as meaningless. Histological assessment by cross sectional area based on lumen and vessel perimeters, assuming these to be circumferences of circles, is usually more accurate but will still give underestimates when the lumen is elliptical or D-shaped, since a circle has the maximum cross sectional area that can be obtained with a given perimeter.

The luminal densitometric readout relates directly to the lumen cross sectional area[13–15] and if this is compared with a densitometric readout from a normal segment of artery then a true cross sectional area percentage stenosis may be obtained from only one *x*-ray view irrespective of the lumen shape and position. This avoids the problem of calibrating the densitometric readings which would be necessary if measurement of the absolute lumen area was required. The problems in being able to do this from a two dimensional coronary arteriogram taken at necropsy, however, are many—notwithstanding those encountered with angiograms taken during life. Nevertheless provided the image analysis techniques used are applicable to soft tissue and background densities by digital subtraction and an *x*-ray film can accommodate the full range of densities encountered in the radio-opaque contrast filled artery, then measurements of true cross sectional area percentage stenosis should be feasible. In practice, however, this is often more difficult than it seems, the contrast obtained in an *x*-ray being dependent not only on concentration of radio-opaque medium but also on *x*-ray exposure time, intensity of *x*-ray beam, and developing of the *x*-ray plate. A further problem is the supposition that the adjacent apparently non-lesional segment of coronary artery is normal. In fact this is not always the case; regular diffuse narrowing may be entirely missed on *x*-ray so that if a severe stenosis is present within a long segment of less severe diffuse narrowing, the severe stenosis may still be underestimated. At present we have no idea of what the normal range of coronary artery calibre is for any given point within the epicardial coronary arterial tree. A definitive assessment must be to measure the flow rate beyond a stenosis, since the answer to "is 75% stenosis in a given vessel more important than 75% stenosis in a vessel twice its size?", begs the question as to what is the normal coronary artery diameter at any given point, and such a question can only be answered from flow studies.

The three dimensional reconstruction of the coronary arterial lumen from densitometric readings of two dimensional angiograms should be feasible provided sufficient $x$-ray planes are examined.[13 14 16] If the stenosed lumen had a circular or ovoid shape then a limited number of views may well be adequate, provided that in this case some calibration is introduced. The more irregular the lumen shape, the greater the number of $x$-ray planes required to enable a reconstruction to be made. The importance of reconstruction may be to detect those lesions which are complicated by thrombosis or plaque fissuring or both and are therefore the more likely to precipitate sudden death or myocardial infarction.

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*Br Heart J* 1986; 55: 140–7

# Improved myocardial lactate extraction after propranolol in coronary artery disease: effected by peripheral glutamate and free fatty acid metabolism

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SUMMARY Ten patients with chronic effort angina and coronary artery disease (luminal diameter reduction >75%) were stressed by atrial pacing (140 beats/minutes) before and 15 minutes after intravenous propranolol (mean dose 7·4 mg). Myocardial substrate exchange of oxygen, blood lactate, plasma free fatty acids, citrate, glucose, glutamate, and alanine as well as coronary sinus blood flow were measured. Coronary sinus blood flow, oxygen consumption, and systemic haemodynamics did not change after propranolol. Propranolol did not influence arterial lactate concentration, and it reduced the arterial concentration of free fatty acid by 37% and increased that of glutamate by 21%. During pacing myocardial lactate extraction increased in all 10 patients; in two lactate release was converted to lactate uptake. Propranolol reduced free fatty acid uptake and increased glutamate uptake during pacing. For both substances the changes in aortocoronary sinus differences or in uptake or both correlated positively with the changes in their delivery to the heart from extracardial sources (arterial concentrations/loads). In the unstressed state before pacing, aortocoronary sinus lactate differences correlated inversely with free fatty acid differences and positively with those of glutamate. During pacing the relation between lactate and glutamate differences remained positive while the inverse correlation between lactate and free fatty acid differences was lost. Myocardial citrate release was halved during pacing and recovery. Propranolol did not influence alanine or glucose exchanges.

An improved myocardial lactate extraction after propranolol administration may be secondary to decreased free fatty acid uptake or increased glutamate uptake or both. In the unstressed state both mechanisms may be of importance. During pacing induced ischaemia, increased glutamate uptake is more likely than reduced free fatty acid uptake to be the mechanism responsible for the improvement in myocardial lactate extraction. The propranolol mediated alterations in myocardial substrate exchanges may reflect the extracardial effects of the drug.

The well established antianginal effect of beta adrenoceptor blocking drugs is attributed to decreased oxyen requirements secondary mainly to a reduced heart rate.[1 2] In addition there is evidence in patients with coronary artery disease of a metabolic effect that improves myocardial carbohydrate utilisation, independently of the haemodynamic actions of such agents.[3 4] Increased myocardial lactate extraction has been reported after administration of beta adrenergic antagonists.[3-5] The antilipolytic effect of beta blockers[6] with subsequent reduction in circulating free fatty acid concentration and hence a reduction in substrate competition, has been proposed as the mechanism responsible for the improved lactate extraction.[4] In the normal heart in which the capacity of free fatty acid oxidation is high and unrestricted this

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Accepted for publication 12 September 1985

mechanism seems of regulatory importance.[7 8] In the ischaemic heart the capacity for free fatty acid oxidation is limited.[9] Therefore a reduction in free fatty acid supply after beta blockade cannot be expected to improve carbohydrate utilisation to the same degree as it does in the normal heart. Myocardial carbohydrate breakdown can proceed only to the extent that oxidation of the glycolytically produced reduced nicotinamide adenine dinucleotide takes place.[10] This occurs indirectly via the malate-aspartate shuttle,[11] and this is in turn dependent on the import of glutamate into the myocardial cell.[12] We have reported positive relations between glutamate uptake and both glucose and lactate uptake in coronary artery disease in the unstressed state.[13]

To elucidate further the mechanisms underlying alterations in myocardial metabolism after beta blockade we have examined myocardial substrate exchanges of lactate, free fatty acids, citrate, glucose, glutamate, and alanine during atrial pacing in patients with coronary artery disease before and after the administration of propranolol.

## Patients and methods

Ten men (mean age 53, range 40–66 years) were studied after their informed consent had been obtained. All had chronic effort angina with ST segment depression (2 to 5 mm) during exercise stress testing. Three patients had had myocardial infarction more than six months before. None had additional heart disease, hypertension, or metabolic disorders. The patients had undergone left ventriculography and coronary angiography a week before the study. Seven patients had important stenoses (a reduction in luminal diameter of >75% that was resistant to glyceryl trinitrate) of three vessels, of two vessels in two patients, and of one vessel in one patient. All except one had stenosis of the anterior descending branch of the left coronary artery. Mean (SD) left ventricular end diastolic pressure was 11 (2) mm Hg and the ejection fraction was 64 (6)%. Antianginal medication except for glyceryl trinitrate (verapamil in five patients, propranolol in three, metoprolol in one, and combined nifedipine and metoprolol in one) was stopped a week before the study; glyceryl trinitrate was allowed up to four hours before the examination.

### PROCEDURE

The patients were examined in the supine position without sedation in the morning after an overnight fast. A Wilton Webster thermodilution pacing catheter was advanced to a midposition in the coronary sinus via an antecubital vein. Coronary sinus blood flow was measured by continuous infusion of saline solution (36 ml/min) for 20–25 seconds for each measurement.[14] A Teflon catheter for arterial blood sampling and pressure measurements was inserted into the distal aorta percutaneously via a femoral artery. The catheters were kept patent by intermittent infusion of saline solution containing heparin (total dose below 300 units).

Coronary sinus pacing was carried out at a constant rate of about 140 beats/minute until intolerable angina occurred of for at least 10 minutes. Propranolol (0·1 mg/kg) (mean (SD) dose 7·4 (0·7) mg) was given intravenously 30 minutes after the end of pacing for two mintues. Fifteen minutes later the patients were stressed by repeated coronary sinus pacing of same duration and rate as during the first pacing period. During the two pacing periods the coronary sinus electrode was maintained in the same position by fluoroscopic control.

During both pacing studies coronary sinus blood flow, heart rate, and blood pressure (Elema Schönander transducer) were determined in triplicate in resting state, twice during pacing after onset of slight angina (in three patients only one measurement was made because severe angina developed), and at three and five minutes into recovery. In each patient haemodynamic measurements and blood sampling were obtained at the same times during the two studies. After separation of samples for the measurement of oxygen saturation, blood samples were collected into heparinised ice cooled glass tubes. Blood was deproteinisated for blood lactate determination and centrifuged for plasma analysis at 4°C. After storage at −80°C for a few days, samples were analysed for concentrations of blood lactate, plasma free fatty acids, plasma glucose, plasma citrate (10 patients), and plasma glutamate and plasma alanine (seven patients) as described elsewhere.[15 16]

### STATISTICAL ANALYSIS

Fractional myocardial substrate extraction was calculated as the aortocoronary sinus difference divided by the arterial concentration multiplied by 100 (%). Net substrate exchange across the heart was calculated from the aortocoronary sinus difference, coronary sinus blood flow, and haematocrit. Data are given as mean (1 SD) or mean and range. The paired two tailed $t$ test and linear regression analysis were used for statistical evaluation. A probability value of <0·05 was considered to be significant.

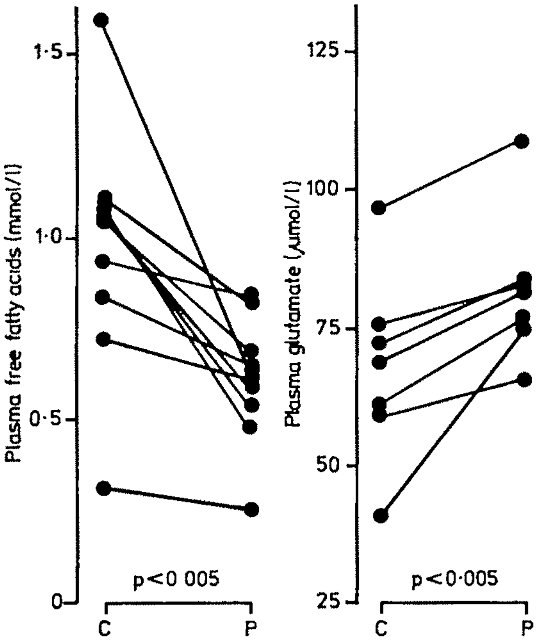

Fig. 1 *Arterial concentrations of plasma free fatty acids and plasma glutamate in control state (C) and after propranolol administration (P) in patients with coronary artery disease. Values are means of seven blood samples obtained throughout each study period*

## Results

In the unstressed state before pacing none of the patients had chest pain. All except for one patient with two vessel disease complained of typical angina pectoris during the first pacing period. The mean pacing time of both periods was 305 seconds (range 60–600 seconds). During repeated pacing after propranolol three patients did not develop chest pain, pacing time to onset of angina was increased by 10–120 seconds (mean 80 seconds) in four patients, and remained unchanged in three patients.

### HAEMODYNAMIC RESULTS

Propranolol administration did not change heart rate, systolic aortic pressure, the rate pressure product, or coronary sinus blood flow. Mean (SD) values before and after propranolol were for heart rate at rest 68 (17) *vs* 69 (11) beats/minute and during pacing 139 (5) *vs* 140 (5) beats/minute. Systolic aortic pressure at rest was 140 (5) *vs* 136 (22) mm Hg and during pacing 130 (23) *vs* 125 (25) mm Hg. Rate pressure product (heart rate multiplied by systolic aortic pressure) at rest was 95 (36) *vs* 94 (21) beats/minute × mm Hg × $10^{-2}$ and during pacing 182 (37) *vs* 178 (39) beats/minute × mm Hg × $10^{-2}$. Coronary sinus blood flow at rest was 119 (37) to 120 (43) ml/minute and during pacing 200 (73) *vs* 182 (62) ml/minute (eight patients only).

After propranolol the aortocoronary sinus oxygen difference increased slightly during pacing, from 119 (9) to 126 (10) ml/l ($p<0·05$), but was unchanged at rest (121 (21) *vs* 123 (13) ml/l). Myocardial oxygen consumption (eight patients) did not change; values before and after propranolol were 15·1 (6·9) *vs* 14·9 (5·5) ml/minute at rest and 24·1 (10·1) *vs* 23·0 (8·1) ml/minute during pacing.

### METABOLIC RESULTS

*Arterial concentrations*

There was no tendency for arterial concentration of metabolites to increase or decrease during each of the two study periods of about 15 minutes. After propranolol the arterial concentrations (mean of concentrations at rest and during pacing and recovery) of plasma free fatty acids decreased by 37% (from 0·98 (0·33) to 0·62 (0·17) mmol/l), increased by 21% for plasma glutamate (from 68 (17) to 82 (14) µmol/l) (Fig. 1), and decreased slightly for plasma alanine (from 222 (77) to 204 (61) µmol/l) ($p<0·05$). No change was found for the other metabolites. Mean arterial concentrations before and after propranolol were—blood lactate 0·78 (0·19) *vs* 0·77 (0·14) mmol/l, plasma glucose 5·59 (0·54) *vs* 5·63 (0·51) mmol/l, and plasma citrate 79 (30) *vs* 82 (25) µmol/l.

*Substrate exchange (Table)*

In the resting state propranolol did not influence substrate exchange except that there was an increased aortocoronary sinus difference in glutamate concentrations.

In the control tests atrial pacing induced a release of lactate across the heart in seven patients, while lactate extraction remained positive in three patients including the one who did not complain of angina. After propranolol myocardial *lactate* extraction increased in all the patients; a mean lactate release of 16 µmol/minute was converted to a mean uptake of 13 µmol/minute. Propranolol reduced *free fatty acid* uptake during pacing and at 5 minutes of recovery, both when this result was calculated as aortocoronary sinus difference and as net uptake. Fractional free fatty acid extraction was reduced at 5 minutes of recovery only. Myocardial *citrate* release was halved during pacing and recovery, both in terms of aortocoronary sinus difference and net release. Aortocoronary sinus *glutamate* differences always increased after propranolol administration, but the net uptake increased only during pacing. Notably, fractional glutamate extraction remained virtually unchanged. Propranolol did not influence

Table *Myocardial exchange of substrates before and after propranolol administration to patients undergoing atrial pacing*

| | *Rest* | *Pacing* | *Recovery* | |
|---|---|---|---|---|
| | | | *3 min* | *5 min* |
| Aortocoronary sinus lactate difference (mmol/l) (n = 10) | | | | |
| Control | 0·15 (0·09) | −0·11 (0·19) | 0·06 (0·17) | 0·14 (0·12) |
| Propranolol | 0·19 (0·10) | 0·04 (0·17) | 0·20 (0·10) | 0·22 (0·09) |
| | NS | p<0·005 | p<0·05 | p<0·02 |
| Myocardial lactate extraction (%) (n = 10): | | | | |
| Control | 20·9 (14·7) | −15·6 (27·2) | 9·9 (21·0) | 19·2 (15·2) |
| Propranolol | 27·4 (14·5) | 4·4 (22·0) | 26·0 (13·9) | 29·3 (13·3) |
| | NS | p<0·005 | p<0·05 | p<0·01 |
| Myocardial lactate uptake (μmol/min) (n = 8): | | | | |
| Control | 18·1 (11·0) | −15·9 (28·8) | 11·1 (28·7) | 19·3 (20·8) |
| Propranolol | 21·1 (11·3) | 12·8 (25·5) | 23·1 (14·1) | 27·3 (12·3) |
| | NS | p<0·02 | NS | NS |
| Aortocoronary sinus FFA difference (mmol/l) (n = 10): | | | | |
| Control | 0·15 (0·13) | 0·16 (0·16) | 0·13 (0·09) | 0·15 (0·11) |
| Propranolol | 0·11 (0·09) | 0·05 (0·10) | 0·09 (0·10) | 0·01 (0·09) |
| | NS | p<0·02 | NS | p<0·02 |
| Myocardial FFA extraction (%) (n = 10): | | | | |
| Control | 19·4 (7·5) | 15·1 (11·9) | 15·0 (12·2) | 16·2 (12·0) |
| Propranolol | 22·3 (15·2) | 6·8 (18·0) | 13·4 (16·6) | 0·5 (18·2) |
| | NS | NS | NS | p<0·05 |
| Myocardial FFA uptake (μmol/min) (n = 8): | | | | |
| Control | 12·2 (6·9) | 21·1 (24·2) | 9·6 (8·7) | 11·7 (9·6) |
| Propranolol | 8·3 (6·5) | 7·2 (14·2) | 5·3 (7·7) | 0·7 (6·1) |
| | NS | p<0·05 | NS | p<0·02 |
| Aortocoronary sinus citrate difference (μmol/l) (n = 10): | | | | |
| Control | −5 (2) | −5 (3) | −8 (3) | −8 (4) |
| Propranolol | −4 (2) | −2 (2) | −4 (5) | −4 (7) |
| | NS | p<0·01 | p<0·05 | p<0·05 |
| Myocardial citrate release (μmol/min) (n = 8): | | | | |
| Control | 0·35 (0·21) | 0·61 (0·36) | 0·59 (0·22) | 0·56 (0·36) |
| Propranolol | 0·28 (0·17) | 0·22 (0·26) | 0·16 (0·40) | 0·25 (0·20) |
| | NS | p<0·05 | p<0·02 | p<0·05 |
| Aortocoronary sinus glutamate difference (μmol/l) (n = 7): | | | | |
| Control | 34 (7) | 19 (4) | 28 (5) | 30 (8) |
| Propranolol | 43 (7) | 32 (8) | 39 (6) | 41 (9) |
| | p<0·01 | p<0·01 | p<0·005 | p<0·02 |
| Myocardial glutamate extraction (%) (n = 7): | | | | |
| Control | 49·9 (7·8) | 28·9 (8·1) | 45·0 (12·8) | 46·5 (16·1) |
| Propranolol | 52·0 (10·6) | 38·7 (11·4) | 49·4 (10·2) | 51·0 (12·4) |
| | NS | NS | NS | NS |
| Myocardial glutamate uptake (μmol/min) (n = 7) | | | | |
| Control | 2·39 (0·87) | 2·28 (0·94) | 2·31 (1·13) | 2·37 (1·23) |
| Propranolol | 3·00 (1·22) | 3·21 (0·58) | 2·63 (1·08) | 2·61 (1·18) |
| | NS | p<0·005 | NS | NS |
| Aortocoronary sinus alanine difference (μmol/l) (n = 7): | | | | |
| Control | −20 (9) | −17 (8) | −21 (9) | −21 (10) |
| Propranolol | −20 (7) | −15 (9) | −22 (10) | −19 (8) |
| | NS | NS | NS | NS |
| Myocardial alanine release (μmol/min) (n = 7): | | | | |
| Control | 1·41 (0·66) | 1·91 (0·95) | 1·70 (1·01) | 1·57 (0·85) |
| Propranolol | 1·41 (0·76) | 1·58 (1·03) | 1·55 (1·08) | 1·23 (0·99) |
| | NS | NS | NS | NS |

Values are means (SD). In each patient values were determined in triplicate at rest and once at the end of pacing. FFA, free fatty acids.

myocardial *alanine* exchange at any time. Neither could any change in *glucose* exchange be demonstrated; values during pacing before and after propranolol were: aortocoronary sinus difference 0·13 (0·14) *vs* 0·14 (0·12) mmol/l; fractional extraction 2·4 (2·7) *vs* 2·4 (2·4)%; net uptake 15·6 (17·0) *vs* 17·3 (18·4) μmol/minute.

### *Changes in lactate, free fatty acid, and glutamate uptake in relation to changes in their arterial concentrations (Fig. 2)*

The propranolol mediated changes in aortocoronary sinus differences of lactate correlated positively with the changes in its arterial concentration at rest but not during pacing. The same tendency was found after coronary sinus blood flow measurements were included; correlation coefficients between the changes in uptake and in load (arterial concentration multiplied by flow) of lactate were (eight patients) rest and pacing together, r = 0·15 (NS); rest, r = 0·56 (NS); pacing, r = 0·23 (NS). The decrease in aortocoronary sinus free fatty acid difference correlated positively with the fall in its arterial concentration when data at rest and during pacing

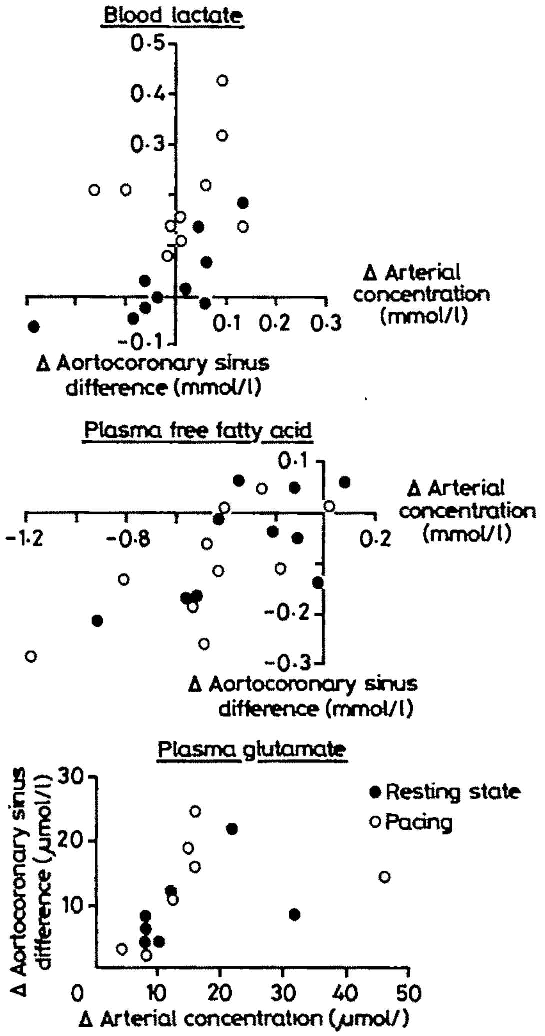

Fig. 2 *Relations between the change in each patient after propranolol in aortocoronary sinus differences of blood lactate, plasma free fatty acids, and plasma glutamate, and the change in their arterial concentrations. Each Δ value is the value after propranolol minus that in control state. Blood lactate: all measurements $r=0{\cdot}06$, NS, $n=20$; rest $r=0{\cdot}71$, $p<0{\cdot}05$, $n=10$; pacing $r=0{\cdot}14$, NS, $n=10$. Plasma free fatty acids: all measurements $r=0{\cdot}67$, $p<0{\cdot}01$, $n=20$; rest $r=0{\cdot}58$, NS ($p<0{\cdot}1$); $n=10$; pacing $r=0{\cdot}70$, $p<0{\cdot}05$, $n=10$. Plasma glutamate: all measurements $r=0{\cdot}39$, NS, $n=14$; rest $r=0{\cdot}45$, NS, $n=7$; pacing $r=0{\cdot}36$, NS, $n=7$.*

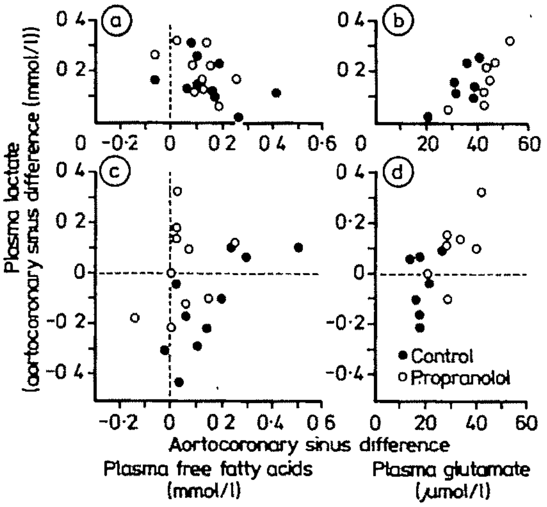

Fig. 3 *Relations between aortocoronary sinus differences of blood lactate and corresponding values for plasma free fatty acids and plasma glutamate at rest (a, b) and during pacing (c, d) before and after administration of propranolol.*
*(a) All measurements $r=-0{\cdot}45$, $p<0{\cdot}05$, $n=20$; control state $r=-0{\cdot}38$, NS, $n=10$; propranolol $r=-0{\cdot}50$, NS, $n=10$.*
*(b) All measurements $r=0{\cdot}63$, $p<0{\cdot}05$, $n=14$; control state $r=0{\cdot}70$, NS ($p<0{\cdot}1$), $n=7$; propranolol $r=0{\cdot}81$, $p<0{\cdot}05$, $n=7$.*
*(c) All measurements $r=0{\cdot}28$, NS, $n=20$; control state $r=0{\cdot}73$, $p<0{\cdot}05$, $n=10$; propranolol $r=0{\cdot}23$, NS, $n=10$.*
*(d) All measurements $r=0{\cdot}69$, $p<0{\cdot}01$, $n=14$; control state $r=0{\cdot}35$, NS, $n=7$; propranolol $r=0{\cdot}64$, NS, $n=7$.*

were combined, during pacing, and insignificantly at rest. Correlation coefficients for the changes in free fatty acid uptake versus in load were: rest and pacing together, $r=0{\cdot}62$ ($p<0{\cdot}01$); rest; $r=0{\cdot}24$ (NS); pacing, $r=0{\cdot}54$ (NS). Figure 2 shows that there was a tendency towards a positive relation between the increase in aortocoronary sinus glutamate difference and in its arterial concentration. For plasma glutamate changes in uptake versus in load the relation (seven patients) became significantly positive. These were the correlation coefficients: for rest and pacing together, $r=0{\cdot}75$ ($p<0{\cdot}01$); for rest, $r=0{\cdot}90$ ($p<0{\cdot}01$); and for pacing, $r=0{\cdot}69$ (NS) ($p<0{\cdot}1$).

Thus, during pacing the increase in extraction of lactate after propranolol did not correlate with changes in its supply to the heart. Both the reduction in free fatty acid and the increase in glutamate uptake after propranolol were positively related to the changes in their delivery from extracardial sources.

### *Interrelations between lactate and free fatty acid and glutamate exchanges (Fig. 3)*

In the unstressed state before pacing values before and after propranolol for aortocoronary sinus lactate difference correlated inversely with free fatty acid differences and positively with glutamate differences (Fig. 3a and b). During pacing the lactate differences remained positively related to those of glutamate (Fig. 3d). Because of the limited number of patients studied, the same tendencies were found only when data before and after propranolol were considered separately. The relation between aortocoronary sinus lactate and glutamate differences at rest after propranolol, however, was statistically significant. The inverse relation between aortocoronary sinus differences between lactate and free fatty acids at rest was lost during pacing (Fig. 3c); but when values before propranolol were examined separately, the aortocoronary sinus lactate and free fatty acid differences correlated positively during pacing.

## Discussion

We have examined the mechanisms that may underlie changes in myocardial metabolism after propranolol administration to patients with coronary artery disease.

As in previous studies of beta blockade during atrial pacing we found that myocardial oxygen uptake remained unchanged.[3 4 17] Determinants of myocardial oxygen consumption include heart rate, left ventricular contractility, and wall tension.[18] Heart rate was controlled by pacing. The propranolol induced decrease in contractility and oxygen uptake was probably counterbalanced by left ventricular dilatation with a subsequent increase in wall tension.[2 4] Coronary sinus blood flow and systemic haemodynamics were not influenced by propranolol. Beta adrenergic blockers may cause regional redistribution of myocardial blood flow in favour of ischaemic areas.[19] This effect has been reported to be eliminated during pacing.[20] Thus, the changes in substrate exchange across the heart found in the present study cannot be attributed to the haemodynamic effects of propranolol.

Despite unchanged heart work, there was evidence of an antianginal effect of propranolol. After the drug three patients did not develop angina, and pacing time until angina developed increased in four and was unchanged in three. Beta blockade has not consistently been reported to have a beneficial effect on clinical signs of pacing induced ischaemia. This is probably the result of methodological differences between studies. In particular, patients may have been insufficiently stressed.[4 17] In our study all except one complained of angina before propranolol. In this patient, the effect of pacing at 140 beats/minute for 10 minutes may have been too low to induce ischaemia. In seven of the ten patients a release of lactate across the heart indicated the development of myocardial ischaemia during control pacing.

The energy requirements of the normal heart are met by oxidation of free fatty acids, glucose, and lactate. Lactate (by oxidation) and glucose (by glycolysis) are both converted to pyruvate. Oxidation of pyruvate is controlled at the site of pyruvate dehydrogenase. Free fatty acid catabolism inhibits pyruvate dehydrogenase by causing intracellular accumulation of acetyl-CoA and reduced nicotinamide adenine dinucleotide.[21] Reduction of myocardial free fatty acid uptake and oxidation by nicotinic acid infusion augments glucose and lactate uptake of the normal human heart.[7] The peripheral antilipolytic effect of propranolol[6] leading to lowered arterial free fatty acid concentration with subsequent reduced free fatty acid oxidation and increased pyruvate dehydrogenase activity has been proposed as the mechanism underlying the augmented carbohydrate utilisation of the ischaemic heart after administration of the drug.[4]

Before pacing all patients had net lactate extraction, and none complained of chest pain. Propranolol did not change arterial lactate concentration. Yet, after the drug, changes in aortocoronary sinus lactate differences showed a significant positive relation to the changes in arterial lactate concentration at rest (Fig. 2), confirming that myocardial extraction of lactate is to some extent determined by supply.[22] The inverse relation between aortocoronary sinus lactate and free fatty acid differences at rest (Fig. 3a) is consistent with the idea of competition between lactate and free fatty acid for entry into the citric acid cycle, though the increase in lactate extraction after propranolol did not reach statistical significance in our study.

The findings during pacing of increased myocardial lactate extraction and decreased net free fatty acid uptake after propranolol confirm the results of others.[3-5] During pacing the changes in aortocoronary sinus lactate differences did not correlate with the changes in arterial lactate concentration (Fig. 2). After administration of atenolol, Thompson *et al* found that changes in myocardial lactate extraction and arterial free fatty acid concentration were inversely related both at rest and during atrial pacing.[4] Only four of their eleven patients developed angina. They included all values obtained during gradual increases in heart rate to demonstrate the inverse relation between lactate extraction and free fatty acid supply during pacing. We were unable to demonstrate an inverse relation between aortocoronary sinus lactate and free fatty acid differences at end of pacing after patients had been stressed at a constant high rate (Fig. 3c) This, taken with the decrease in free fatty acid oxidation during ischaemia,[9] raises the question of whether the reduced free fatty acid uptake at end of pacing after propranolol led to a further reduction in free fatty acid oxidation of a magnitude sufficient to explain the observed improvement in lactate extraction.

This suggestion is subject to limitations. Extraction of both lactate and free fatty acids decreases during ischaemia. Thus, at end of pacing an interrelation between lactate and free fatty acid aortocoronary sinus differences does not necessarily reflect substrate competition; it may merely reflect the relation between different markers of ischaemia, which may also explain the positive correlation between lactate and free fatty acid during control pacing before propranolol administration. Further, we measured net chemical free fatty acid uptake only. Experiments with labelled palmitate have demonstrated myocardial lipolysis,[23] which is inhibited by propranolol.[6] Although we did not measure changes in myocardial lipolysis, a reduction in myocardial free fatty acid oxidation after propranolol could explain the fall in myocardial citrate release during pacing and recovery. Oxidation of free fatty acids is the main determinant of myocardial citrate release.[15] Citrate restriction of the glycolytic enzyme phosphofructokinase is an additional mechanism by which free fatty acids reduce utilisation of carbohydrate by the heart.[24] Because propranolol reduced myocardial citrate release an increase in glucose uptake, as found in animal studies, is likely.[25] The small absolute glucose aortocoronary sinus differences did not allow us to show this.

Reoxidation of glycolytically produced reduced nicotinamide adenine dinucleotide is among further mechanisms that may be important in the regulation of myocardial utilisation of lactate (and glucose).[10] The inner mitochondrial membrane is impermeable to reduced nicotinamide adenine dinucleotide. Transfer of reducing equivalents, formed by reduction of cytosolic nicotinamide adenine dinucleotide, for oxidation in the mitochondrial electron transport chain occurs mainly indirectly via the malate-aspartate cycle when glucose is the substrate and probably exclusively by the mechanism when lactate is the substrate.[11 26] Flux through the shuttle is partly regulated by cytosolic glutamate concentration,[26] and requires import of glutamate.[12] An augmented myocardial glutamate supply may facilitate lactate extraction.

Our study demonstrates an increased arterial glutamate concentration after administration of propranolol. The underlying mechanisms are unknown. There was a consistent increase in aortocoronary sinus glutamate differences in the present study. Fractional extraction, however, did not change. The propranolol induced changes in aortocoronary sinus differences and in arterial concentrations tended to be positively related (Fig. 2). There was a positive statistically significant correlation between changes in glutamate uptake and load (arterial concentration multiplied by flow). Therefore the augmented extracardial supply of glutamate alone seems to be responsible for the increase in glutamate uptake across the heart. The findings that aortocoronary sinus lactate and glutamate differences correlated positively at rest and at end of pacing (Fig. 3b and d) accord with the suggestion that an increased myocardial glutamate uptake is a possible mechanism for increasing lactate extraction in the unstressed state as well as at end of pacing. Although there is a physiological basis for these correlations, the proposed causality must be evaluated. Aortocoronary sinus lactate and glutamate differences decrease during ischaemia.[16] Thus, as in the case of lactate versus free fatty acid differences, the relation between lactate and glutamate differences at end of pacing need not reflect an interaction between substrates; it may represent a relation between two markers of ischaemia.

Myocardial glutamate uptake is greater in patients with coronary artery disease than in normal controls.[13 16] Positron emission tomography has shown a high extraction of glutamate in ischaemic areas of the human heart despite reduced blood flow.[27] Fractional extraction of glutamate is two to three times higher than that of lactate (Table). In one patient a global extraction of 70% suggests almost complete extraction of glutamate by the ischaemic zones. Thus, supply of glutamate may be a limiting factor for the maintenance of carbohydrate use.

There was no change in myocardial alanine release after propranolol; the slight fall in arterial alanine concentration may have been the result of an increase in the duration of the overnight fast during the second pacing study.[28] Alanine release in part reflects alanine production from transamination of glutamate with pyruvate.[29]

The reduction in regional blood flow in ischaemic heart disease means that the direct effect of peripherally administered drugs upon the myocardium is likely to be moderate. In our study myocardial free fatty acid was reduced and glutamate uptake was increased after propranolol; findings which could be related to changes in the supply of each of the two substances, and thus be explained by extracardial actions of the drug—that is inhibition of peripheral lipolysis in the case of free fatty acid uptake and augmentation of the circulating concentration of glutamate. Both mechanisms seem to be important for improving myocardial lactate extraction in unstressed state. During pacing induced tachycardia the increased glutamate uptake may be of greater importance. Because myocardial oxygen uptake did not change, the results of our study support the idea of a metabolic contribution of propranolol in relieving angina that is additional to its haemodynamic effects.

This study was supported by grants from the Danish Heart Association.

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# Changes in left ventricular function during exercise and their relation to ST segment changes in patients with angina

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SUMMARY The high count sensitivity of the non-imaging nuclear probe affords the possibility of measuring left ventricular ejection fraction continuously during short term interventions. The nuclear probe was used to examine the pattern of change of left ventricular function during dynamic exercise and its temporal relation to ST segment depression in 12 patients with stable exertional angina. After in vivo blood pool labelling with technetium-99m the left ventricular time-activity waveform was detected by the nuclear probe and was continuously recorded on a strip chart. The 15 beat mean ejection fraction and the ST segment level 80 ms after the J point were measured at rest and every 30 seconds during maximal ergometric exercise and during recovery. The mean ejection fraction was 54·3% (range 46–64%) at rest and fell during exercise in all subjects by a mean of 16·8% (range 6–25%). In contrast, in a control group of 16 healthy male volunteers the mean ejection fraction was 55·9% (range 47–64%) at rest and increased in all by a mean of 10·2% (range 3–19%) during exercise. The difference of ejection fraction response to exercise between the patients and controls was due to pronounced increases in relative end diastolic and especially end systolic volumes in the patients. Relative stroke volume differed between patients and controls only at peak exercise. ST segment depression >1 mm developed in 11 of the 12 patients. A decrease of >5% in ejection fraction occurred within 1 minute of starting exercise in nine of the 12, and in 11 patients it preceded the beginning of ST depression. In most of this selected group of patients the ejection fraction had fallen during exercise before the appearance of ischaemic electrocardiographic changes.

Invasive studies in animals indicate that myocardial ischaemia produces impairment of left ventricular function that can be detected before the appearance of ischaemic changes in the electrocardiogram.[1-3] Non-invasive studies in man with gated equilibrium blood pool methods[4-6] and serial first-pass gold-195m angiography[7] have confirmed that an abnormal response of the ejection fraction to exercise is a sensitive indicator of coronary heart disease and its outcome.[8] These methods suffer from the disadvantage of a slow response-time, making precise temporal correlations difficult. The non-imaging nuclear probe used in the beat to beat mode permits the rapid detection of changes in left ventricular function[9] and can be used continuously during exercise and other interventions.[10 11]

We have used this technique to examine the temporal relation between the onset of left ventricular dysfunction and the appearance of electrocardiographic evidence of myocardial ischaemia during dynamic exercise in patients with stable angina pectoris due to documented obstructive coronary artery disease.

## Patients and methods

We studied 12 patients (10 male, 2 female), mean age 63·2 years (range 50–71), with stable angina pectoris that was reproducible on repeated treadmill testing and was associated with ischaemic ST segment de-

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Accepted for publication 30 September 1985

pression. Coronary artery disease was documented by selective arteriography within 30 days of the study in all cases: three patients had single vessel, three had two vessel, and six had three vessel disease. Two had a documented previous myocardial infarction; angina pectoris had been present for a mean of 25·3 (range 6–48) months. Antianginal medication before the study consisted of a calcium ion antagonist in seven patients, long acting nitrate in three, and a beta blocker in two.

Previous antianginal medication was withdrawn gradually, long acting nitrates over at least 48 hours and other drugs over at least 14 days. The patients rested semi-supine for 30 minutes before the study. During this time the blood pool was labelled by means of stannous pyrophosphate and technetium-99m (740 MBq). Thyroid uptake of technetium was blocked by parenteral sodium perchlorate (200 mg).

The patients performed graded exercise on a reclining cycle in the 25° semisupine position on a specially constructed ergometer. After they had started to cycle against zero resistance the workload was gradually increased over 15 seconds to 150 kilopond metres per minute (25 W) (kpm/min). This was to minimise the initial isometric component of exercise. The workload was gradually increased every three minutes by 150 kpm/min (25 W) and exercise was continued until symptoms appeared.

### LEFT VENTRICULAR FUNCTION MEASUREMENT

We used the non-imaging nuclear probe (Nuclear Stethoscope, Bios Inc.) to detect left ventricular time-activity and we established the left ventricular and background regions of interest by means of operating algorithms and techniques described elsewhere.[12 13] These regions of interest were marked on the chest surface with ink and the position of the probe was maintained by hand throughout the study

The unprocessed signal from the scintillation detector was also fed directly (bypassing the Nuclear Stethoscope's computer) to a signal filter which reduced artefact (but did not distort the peaks and troughs of the waveform) and thence to a Watanabe strip-chart recorder with paper running at 100 mm per minute. A record of each study was also stored on magnetic tape.

We used a ruler to draw a line through the mean background counts, and the end diastolic counts were measured by hand from this line. The ejection fraction (calculated as the mean stroke counts divided by the mean end diastolic counts over the last 15 beats of each 30 second interval) was measured

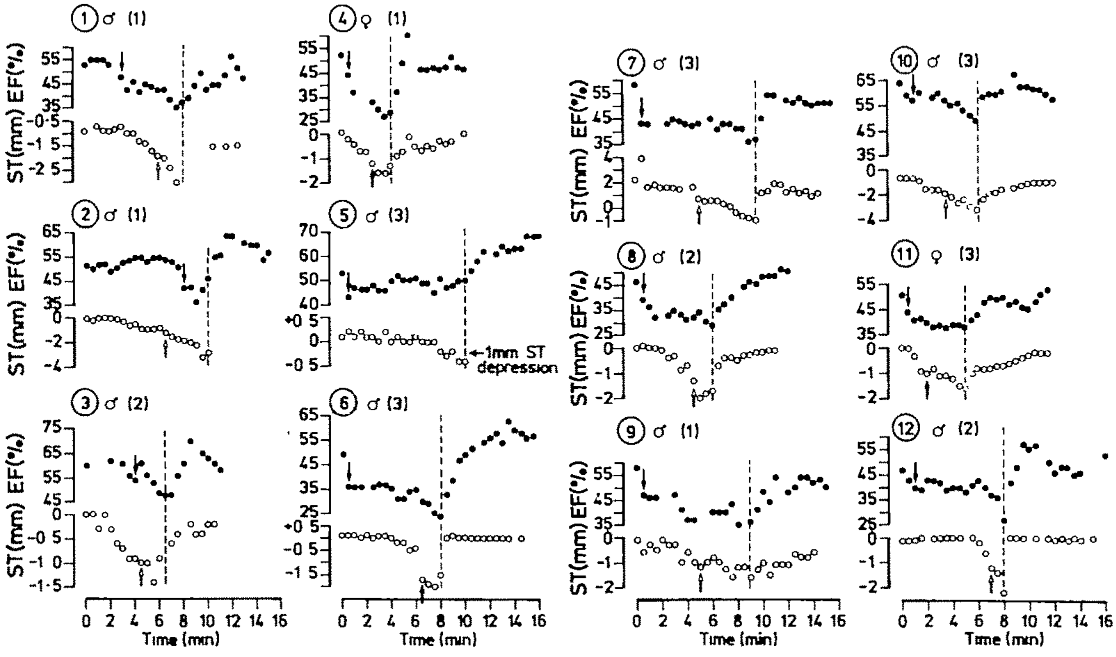

Fig. 1 *Left ventricular ejection fraction (EF) in per cent (closed circles) and ST segment level in mm (open circles) in 12 patients at 30 second intervals during maximal exercise and during recovery. Some data points are missing for technical reasons Patients' study number, sex, and the number of angiographically diseased coronary vessels are indicated. The vertical interrupted line in each graph represents the end of exercise. The closed arrows indicate the time of onset of a 5% (absolute) fall in ejection fraction. The open arrows indicate the time at which 1 mm ST depression developed relative to electrocardiogram at rest.*

immediately before, during, and for five to six minutes after exercise. Extrasystoles and cycles immediately after an extrasystole were rejected. Background was corrected during the third minute of the first stage of exercise and the third minute of recovery.

Bipolar electrocardiographic leads CM5 and CC5 were recorded on a Marquette three channel recorder and ST segment displacement was measured 80 ms after the J point, in whichever lead showed the greatest degree of ST depression. The ST level was measured to an accuracy of 0·1 mm from the stable isoelectric baseline connecting successive PR intervals. The mean figure for three consecutive beats was measured every 30 s.

### CONTROL SUBJECTS

We also studied 16 male volunteers (mean age 37·6 years, range 27–44). None had a history suggestive of cardiovascular disease and all had a normal electrocardiogram both at rest and on maximal treadmill exercise. They followed the same exercise protocol as the patients and the ejection fraction was measured every 60 s.

## Results

The symptoms causing patients to stop exercising were angina in 10 and dyspnoea and fatigue in one each. The patients' mean exercise time was 7·5 minutes (range 4·0–10·5) and the workloads achieved were 300 kpm/min (50 W) in five, 450 kpm/min (75 W) in six, and 600 kpm/min (100 W) in one. All but one patient developed ST segment depression of > 1mm relative to the resting value (mean − 1·8 mm, range −0·6 to −3·2). All the control subjects reached a workload of 450 kpm/min (75 W) and five achieved 600 kpm/min (100 W). All stopped exercise because of fatigue, and none developed ST segment depression. Some of the ST segment data during recovery were lost for three patients (cases 1, 2, and 5 in Fig. 1) for technical reasons. The individual

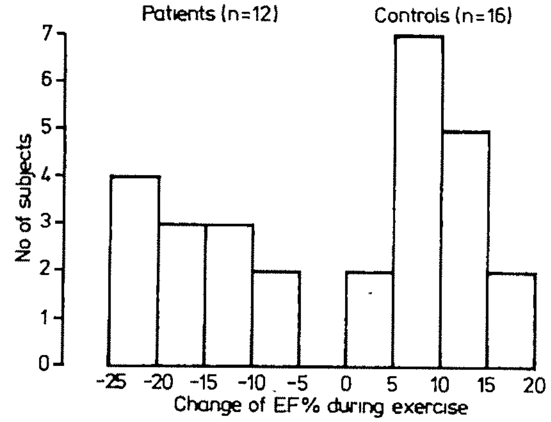

Fig. 3 *Percentage change in left ventricular ejection fraction during exercise in 12 patients and 16 normal controls.*

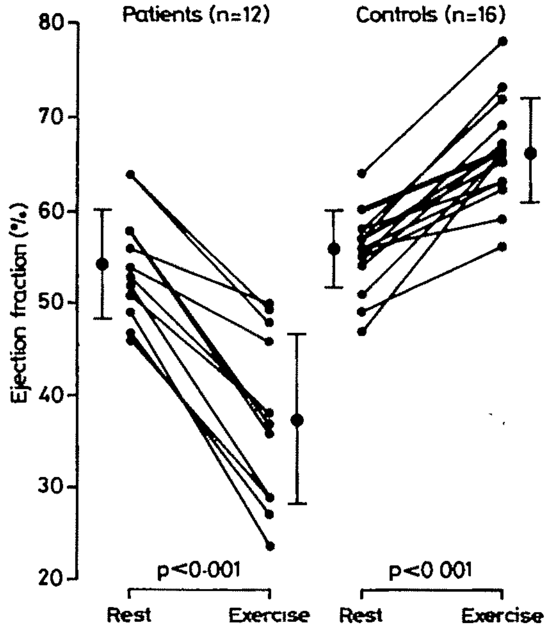

Fig. 2 *Individual ejection fraction values for the controls and the patients at rest and at peak exercise.*

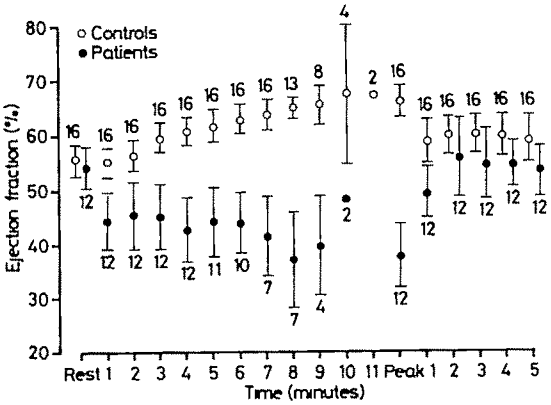

Fig. 4 *Mean left ventricular ejection fraction in patients (closed circles) and controls (open circles) at rest and at each minute during exercise and recovery. Vertical bars represent 95% confidence intervals and the adjoining numbers indicate the number of observations contributing to each data point. Fewer patients than normal subjects attained the higher workloads. Peak values include different workloads. Statistically significant divergence between patients and normal subjects occurred within one minute of the start of exercise and persisted until two minutes into recovery.*

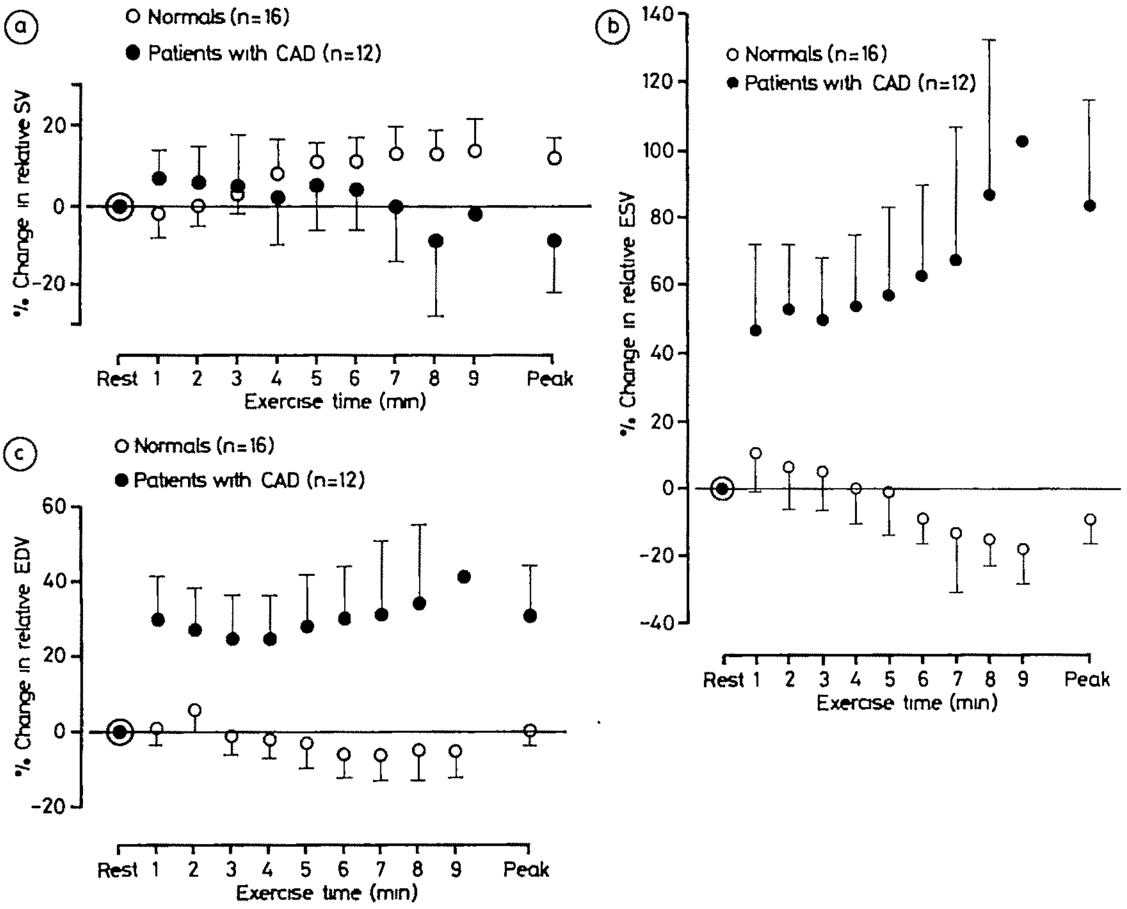

Fig. 5 *Mean per cent change relative to rest each minute during supine cycle ergometry for (a) stroke volume (SV), (b) end systolic volume (ESV), and (c) end diastolic volume (EDV). Symbols as in Fig. 4. CAD, coronary artery disease.*

resting and peak exercise ejection fraction values are shown for controls and patients in Fig. 2.

The mean ejection fraction of the 12 patients was 54·3% (range 46%–64%) at rest and during exercise this decreased in all (mean 16 8%, range 6%–25%) (Fig. 3). In the controls the mean ejection fraction was 55·9% (range 47%–64%) at rest and this increased during exercise in all (mean 10 2, range 3%–19%). The mean values of ejection fraction at rest and at each minute during exercise and recovery in both patients and controls are shown in Fig. 4. The ejection fraction fell in both groups during the first minute of exercise. The fall in the control group was not statistically significant and was reversed as exercise continued. The ejection fraction at one minute of exercise was significantly lower in the patient group than in the controls, and this difference was maintained throughout exercise and until 2 minutes into recovery. The ejection fraction fell by more than 5% absolute in all patients; in nine this fall occurred within the first minute of exercise and in seven within 30 seconds.

Fig. 5 shows the percentage change of the mean end diastolic, end systolic, and stroke volume each minute during exercise and at peak exercise relative to the resting values. The relative end diastolic and end systolic volumes of patients and controls diverged within the first minute of exercise whereas relative stroke volume did not differ until peak exercise, when the patients' stroke volume had decreased relative to that of the controls. Mean end diastolic volume changed little (+0·5% relative to rest) in the normal controls (increased in nine, unchanged in three, decreased in four at peak exercise). Thus the increase (+12%) of mean stroke volume (increased in 15, decreased in one subject) and ejection fraction was due to a decrease (−9%) of end systolic volume (10 out of 16 subjects). By contrast both diastolic and

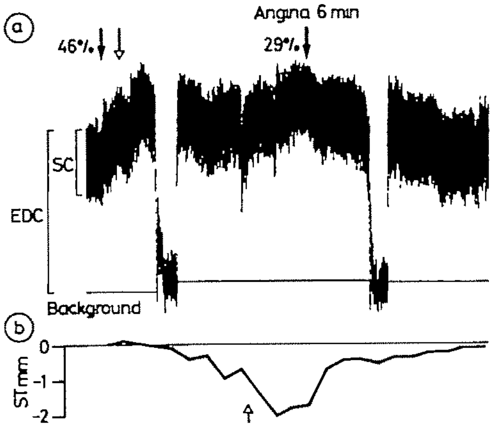

Fig. 6 *Exercise test in a man of 63. (a) Time-activity curve (compressed form, paper speed 10 mm per minute) at rest, during exercise, and after exercise. The start and end of exercise are indicated by closed arrows and the per cent values are the ejection fraction at rest and peak exercise. The open arrow indicates when ejection fraction fell by 5% absolute. The probe was moved to background at rest, during the first stage of exercise, and during recovery. Blips are seen in the time-activity waveform when the patient coughed. (b) ST segment trend with the time of onset of 1 mm depression relative to the electrocardiogram at rest indicated by an open arrow. EDC, end diastolic counts; SC, stroke counts*

systolic volumes increased (mean increases 31% and 84% respectively) in all 12 patients at peak exercise, and mean stroke volume decreased slightly (mean fall 9%; decreased in seven, unchanged in one, increased in four), resulting in pronounced reductions of ejection fraction in all.

In 11 of the 12 patients the ejection fraction had decreased by 5% absolute before the appearance of 1 mm ST segment depression (Fig. 1), including the one man who did not develop 1 mm ST depression at any time.

Background counts increased during exercise and then returned to the resting level during recovery in 10 of the 12 patients. The compressed record of the time-activity waveform of a representative patient is shown in Fig. 6 with the ST segment trend plotted below.

## Discussion

The accuracy of the non-imaging nuclear probe for measuring left ventricular ejection fraction at rest is well established[13,14] and has been validated in our laboratory.[15] We have also compared the probe measurements of ejection fraction at peak semisupine cycle exercise with the results obtained with a digital gamma camera and we found good agreement between the methods.[11] The high count sensitivity of the probe permits beat to beat data acquisition and thus detection of rapidly occurring changes in left ventricular function. The maintenance of the probe over the left ventricular region of interest requires skill on the part of the operator,[12,14] particularly during dynamic exercise,[11,13] but with experience continuous detection of left ventricular time-activity is possible even during maximal dynamic exercise. The stability of the exercising subject's chest was maintained in this study by careful attention to the seat position and the distance from the seat to the cycle pedals. The probe method is simpler than the first pass gold technique and avoids the need for repeated injections of an expensive radionuclide and the use of a digital or multicrystal gamma camera. It has the disadvantages, however, of not providing information about wall motion abnormalities and of requiring exercise to be performed in the supine or semisupine position.[16]

Previous studies have suggested that a few patients with coronary artery disease increase their ejection fraction during supine exercise whereas in many the ejection fraction does not change during exercise.[4,6,17] In all our patients the ejection fraction had fallen by at least 6% (absolute) at peak exercise. This difference can be explained by the selection criteria for our patients, all of whom had established angina and ST depression on treadmill exercise testing and most of whom had multivessel coronary artery disease. Higginbotham *et al* reported that a fall of ejection fraction during upright exercise identified a group of coronary patients with a high mortality during subsequent follow up.[18]

There was a consistent pattern of change of ejection fraction during exercise in our patients with coronary artery disease (Fig. 1). In nine of the 12 patients the ejection fraction decreased by at least 5% absolute within one minute of the start of exercise and in all but one this decrease became more pronounced as exercise progressed. In the remaining three patients the fall in ejection fraction was delayed until 3, 4, and 8·5 minutes of exercise. Even in these patients, however, a further decrease of ejection fraction occurred as exercise continued. Thus our results do not confirm the variability in the evolution of ejection fraction response to upright exercise observed by Wackers and coworkers[7] or that noted by Brady *et al* in response to supine exercise.[4] These workers found increases in ejection fraction during exercise in some patients; the relatively homogeneous response of our patients was probably the result of our selection criteria.

The initial fall of ejection fraction at the start of exercise in most of our patients is worthy of comment, particularly since there was a smaller and statistically non-significant fall in the controls (Fig. 4). This is probably related to the inevitable isometric component inherent in the start of semisupine cycle exercise. Isometric exercise has been shown to induce a fall in ejection fraction in normal subjects[19] as well as patients with coronary artery disease[20] Secondly the increase in venous return which occurs at the onset of dynamic exercise is greater and therefore causes a more pronounced rise in end diastolic volume in the supine position. The fact that other workers have not reported a decrease of ejection fraction during supine exercise in normal subjects may be due to their not recording ejection fraction during the first minute of exercise, since this can be done only with the non-imaging nuclear probe; the ejection fraction at the first minute of upright exercise has been measured by the gold-195m first pass technique.[7]

The fact that the ejection fraction of patients with coronary artery disease was significantly less than that of the controls after only one minute of exercise suggests that the difference could be due to the early onset of ischaemia, probably caused by the sudden increase in afterload that results from the isometric component inherent in ergometric exercise. The rise in left ventricular end diastolic pressure at the start of exercise in patients with ischaemic heart disease is well documented[21] and supports the suggestion that the rapid deterioration of left ventricular function in patients as compared with controls may be related to myocardial ischaemia.

The observation that left ventricular dysfunction due to myocardial ischaemia can occur in the absence of, or before, the appearance of electrocardiographic changes has been made both by invasive[1-3] and non-invasive means.[22 23] Theroux *et al* showed that impairment of canine myocardial contractility, as measured by microsonometers implanted in the myocardium, could be detected within 15 seconds of ligating the coronary artery supplying that area of myocardium.[24] Similar observations were made by Battler *et al.*[3] Upton *et al* demonstrated a reduction in ejection fraction by first pass radionuclide angiography that was detectable during submaximal upright exercise before the appearance of ST segment depression in 19 of 25 patients who resembled those in the present study.[22] Using exercise M mode and cross sectional echocardiography, Sugishita *et al* obtained similar results from patients performing supine cycle ergometry[23]; however, the reproducibility of exercise echocardiography is questionable.

The decrease of ejection fraction with exercise in the patients was due to a large increase in relative end systolic volume (+84% relative to rest). Relative end diastolic volume also increased but only modestly (+31%). Findings in previous studies of changes in left ventricular volumes during supine exercise in patients with angina by contrast and radionuclide ventriculography were similar, with small decreases in stroke volume, small or no increase in end diastolic volume, and pronounced increases in end systolic volume.[21 25 26] Lahiri *et al* measured left ventricular end diastolic pressure and beat to beat ejection fraction with the nuclear probe during atrial stress pacing in patients with coronary artery disease, and they concluded that the fall in ejection fraction and increase in end diastolic pressure were closely related.[11]

The method of evaluating left ventricular function by the non-imaging nuclear probe gives information not available by any other non-invasive means. Further improvement in this technology[15 27] may lead to a better understanding of the underlying mechanisms of both induced and spontaneous myocardial ischaemia. Further study is required to determine whether the observed rapid fall in ejection fraction in this selected group of patients is truly due to myocardial ischaemia or due to an isometric component inherent in the exercise protocol, whether it is reproducible, and what the underlying haemodynamic alterations may be. These results, however, suggest that impairment of left ventricular function is a more sensitive indicator of myocardial ischaemia than electrocardiographic changes.

We thank Mr John Crawley and Mr David Hinge for valuable assistance.

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*Br Heart J* 1986; 55: 155–61

# Comparison of electrocardiographic and echocardiographic measures of left ventricular hypertrophy in the assessment of aortic stenosis

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SUMMARY One hundred and nineteen patients with a clinical diagnosis of important aortic stenosis were assessed clinically and by electrocardiography and M mode echocardiography to determine the degree of left ventricular hypertrophy. Predicted left ventricular pressure was calculated from two previously described formulas. Comparisons were made between the various methods for assessing left ventricular hypertrophy to see which method most reliably predicted the severity of the stenosis as defined by invasive measurement of left ventricular pressure and peak aortic valve gradient. Direct measurement of left ventricular wall thickness from the echocardiogram, expressed as the mean of septal and posterior wall thickness, was the most accurate predictor ($r=0·75$ for 29 patients with high quality echocardiograms), and surpassed derived indices (left ventricular mass ($r=0·68$) and predicted left ventricular pressure derived from the two formulas ($r=0·39$ and $r=0·68$)) in adults. Echocardiographic results were significantly better than electrocardiographic, but only when the recordings were of very high quality. Average quality echocardiograms were no better than precordial electrocardiographic voltages for predicting the severity of aortic stenosis. The formulas for predicting left ventricular pressure were of more value in children than in adults, but they were still not sufficiently accurate to be predictive in individual cases. Electrocardiographic voltages were more accurate predictors of the severity of aortic stenosis in children than in adults.

The detection of left ventricular hypertrophy has become an important clinical goal, particularly for the diagnosis of aortic valve disease and the assessment of hypertension. There are several methods of evaluating left ventricular hypertrophy—palpation of the apex beat, measurement of numerous electrocardiographic variables, and, more recently, echocardiography—but there is little information about the relative reliability of these various techniques in predicting the severity of aortic stenosis.

This study compares the clinical, electrocardiographic, and echocardiographic assessments of left ventricular hypertrophy with the haemodynamic findings in patients suspected of having important aortic stenosis.

## Patients and methods

One hundred and nineteen patients with a clinical diagnosis of important aortic stenosis were studied at admission for cardiac catheterisation. There were 71 males and 48 females (mean age of 51 years, range 16–76). All patients had undergone clinical assessment, 12 lead electrocardiogram, and M mode echocardiography in addition to cardiac catheterisation. Mean peak systolic gradient across the aortic valve was 68 (35) mm Hg, and mean left ventricular pressure was 197 (41) mm Hg. Patients with bundle branch block, previous myocardial infarction, established hypertension, or important aortic valve regurgitation were excluded.

The presence or absence of left ventricular hypertrophy was assessed clinically by palpation of the cardiac apex with the patient turned on the left side. Two measures of precordial electrocardiographic voltage were used: the Sokolow-Lyon

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Accepted for publication 6 August 1985

index[1] (S-V1+R-V5 or V6$\geqslant$35 mV) and the McPhie index[2] (max S+ max R$\geqslant$45 mV). The presence or absence of appreciable lateral ST depression (>1 mm) was noted. No patient was taking digoxin. Standard M mode echocardiograms were measured with a Numonics analyser (Smith Kline instruments) that allows rapid repeated measurements of the same variable in different cardiac cycles and produces a mean value. At least five measurements were made for each variable. The following were measured by the method recommended by the American Society of Echocardiography[3]: interventricular septal thickness at end systole and end diastole ($IVS_s$ and $IVS_d$); posterior free wall thickness of the left ventricle at end systole and end diastole ($LVW_s$ and $LVW_d$); and left ventricular minor axis dimension at end systole and end diastole ($D_s$ and $D_d$). From these data the following were calculated:

(*a*) Mean left ventricular wall thickness at end systole and end diastole ($mean_s$ and $mean_d$) by dividing the sum of septal and posterior wall thicknesses by two.

(*b*) Diastolic left ventricular mass by the Teichholz formula[4] to derive left ventricular volume (taking the specific gravity of cardiac muscle to be $1{\cdot}05\ g/cm^3$.[5]

$$\text{Mass (g)} = 1{\cdot}05\left(\left(\frac{7}{LVW_d + IVS_d + D_d + 2{\cdot}4}\right) \times (LVW_d + IVS_d + D_d)^3 - \left(\frac{7}{D_d + 2{\cdot}4}\right) \times D_d{}^3\right)$$

(*c*) Predicted left ventricular pressure ($LVP_p$) by two formulas:

$$LVP_p = 225 \times (LVW_s/D_s)\,\text{mm Hg}^6$$

and

$$LVP_p = 6 + 298 \times mean_d/r\,\text{mm Hg}^7$$

where r = is the diastolic cavity radius.

(*d*) Mean rate of circumferential shortening (mean Vcf) was calculated in circumferences per second as a measure of overall left ventricular function from the formula described by Fortuin *et al.*[8]

Patients with reduced left ventricular function (mean Vcf <1 circ/s) were excluded from parts of the analysis as it had been stressed in a previous study that the assumptions necessary for applying the formulas for predicting left ventricular pressure were invalid if left ventricular function was abnormal.[6] Mean Vcf was chosen as the measure of left ventricular function because it was the original measure used by Bennett *et al.*[6] Although there may now be better methods of estimating left ventricular function, in the present study mean Vcf >1 circ/s was a valuable and fairly strict criterion for good left ventricular function, as was shown by subsequent calculation of ejection fraction from the cineangiograms (by digitising end systolic and end diastolic frames). Thus only one of 29 patients with mean Vcf >1 circ/s had an ejection fraction of <50%, and the mean for the group was 67%. All the patients with a mean Vcf >1 circ/s had a normal end systolic dimension on the echocardiogram.

All the echocardiograms were measured regardless of their quality. The technical quality of each echocardiogram was assessed as either good (unquestionably high quality), fair (the sort of quality which would normally be considered acceptable for measurement but which was not quite as clear as the good quality echocardiograms, for example one endocardial boundary poorly defined), or poor. This classification meant that the importance of technical quality in determining the predictive value of echocardiographic measurements could be assessed in the subsequent analysis.

All patients underwent cardiac catheterisation during which peak left ventricular pressure and peak systolic gradient across the aortic valve were measured. These two measurements were correlated with the estimates of left ventricular hypertrophy and predicted left ventricular pressure discussed above. The advantage of using left ventricular pressure as an independent variable is that it circumvents some of the problems associated with coexisting hypertension. Cardiac output was not measured routinely, and although this could have introduced bias in the patients with low cardiac output, part of the subsequent analysis excluded patients with poor left ventricular function (low mean rate of circumferential shortening). None of the patients had important aortic regurgitation on clinical, echocardiographic, or aortographic grounds.

## ANALYSIS OF RESULTS

The ability of the different measures of left ventricular hypertrophy to predict the degree of aortic stenosis (as measured by gradient across the aortic valve or left ventricular pressure) was assessed by calculating sensitivity and specificity, and, in the case of continuous variables, by determining the correlation coefficient as well. To calculate sensitivity and specificity the dividing line between important and non-important aortic stenosis was taken to be a gradient of 50 mm Hg or a left ventricular pressure of 180 mm Hg.

Sensitivity (%)=(true positives correctly diagnosed/total true positives)×100

Specificity (%)=(true negatives correctly diagnosed/total true negatives)×100

Table 1 *Sensitivity and specificity of various measures of left ventricular hypertrophy as predictors either of the gradient across the aortic valve or of left ventricular pressure in patients with aortic stenosis*

| *Predictor* | *Criterion* | *Predicted* | *Sensitivity (%)* | *Specificity (%)* | *Accuracy (%)* | *Group* |
|---|---|---|---|---|---|---|
| Clinical LVH | Present or absent | AVG | 81 | 54 | 68 | 1 |
| | | LVP | 73 | 44 | 58 | 1 |
| ST depression | ST depression >1 mm | AVG | 78 | 73 | 76 | 1 |
| | | LVP | 83 | 61 | 75 | 1 |
| Sokolow-Lyon[1] | S-V1+R-V5/6 ⩾35 mV | AVG | 85 | 31 | 69 | 1 |
| | | LVP | 83 | 24 | 64 | 1 |
| McPhie[2] | Max S+Max R ⩾45 mV | AVG | 74 | 57 | 69 | 1 |
| | | LVP | 77 | 47 | 68 | 1 |
| Mean$_d$ | Mean$_d$ ⩾1·15 cm | AVG | 89 | 73 | 83 | 4 |
| | | LVP | 77 | 81 | 79 | 4 |
| Bennett[6] | LVP$_p$ ⩾180 mm Hg | AVG | 34 | 83 | 60 | 4 |
| | | LVP | 38 | 75 | 59 | 4 |
| Aziz[7] | LVP$_p$ ⩾180 mm Hg | AVG | 33 | 100 | 56 | 4 |
| | | LVP | 38 | 93 | 69 | 4 |

Mean$_d$, mean diastolic left ventricular wall thickness; LVH, left ventricular hypertrophy; AVG, aortic valve gradient; LVP, left ventricular pressure; LVP$_p$, predicted left ventricular pressure. Bennett and Aziz are the two formulas for calculating LVP$_p$.

Accuracy (%)=((positives+negatives correctly diagnosed)/total tested) × 100 (reference[9])

Correlations between the gradient or left ventricular pressure and the various measures of left ventricular hypertrophy were made initially with all the patients included (group 1), and then with subgroups selected from group 1: group 2, all patients with high quality echocardiograms; group 3, those patients with a mean rate of circumferential shortening >1 circ/s (a prerequisite for the application of Bennett's formula)[6]; group 4, those patients with high quality echocardiograms and mean rate of circumferential shortening >1 circ/s; group 5, those patients with fair quality echocardiograms and mean rate of circumferential shortening >1 circ/s.

Although these groupings could only be expected to affect the correlations of the echo-derived variables, identical groups were used to determine the correlation of electrocardiographic variables with the pressure gradient across the aortic valve and left ventricular pressure to avoid the possibility that selection of patients from the total study population might have created unrepresentative groups. A group of 13 children aged less than 16 years was also analysed separately (group 6).

## Results

### CLINICAL ASSESSMENT

Left ventricular hypertrophy detected clinically had a reasonable sensitivity but poor specificity (Table 1).

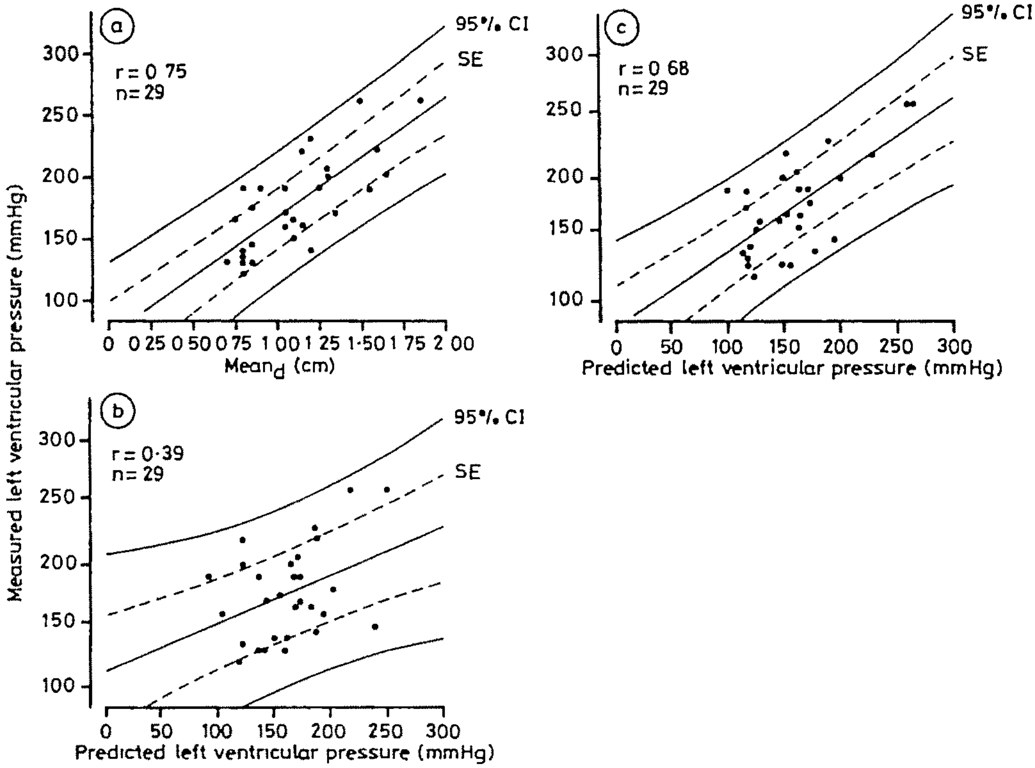
### PREDICTION OF SEVERITY OF AORTIC STENOSIS BY ELECTROCARDIOGRAM

Table 1 gives the sensitivity and specificity for the

Table 2 *Correlation coefficients for relations between measures of left ventricular hypertrophy and the pressure gradient across the aortic valve or left ventricular pressure*

| | | *Group* | | | | | |
|---|---|---|---|---|---|---|---|
| *Measure of LVH* | *AVG or LVP* | *1 (n=119)* | *2 (n=50)* | *3 (n=62)* | *4 (n=29)* | *5 (n=25)* | *6 (n=13)* |
| S-V1 + R-V5/6 | AVG | 0·27 | 0·42 | 0·12 | 0·34 | 0·34 | 0·32 |
| | LVP | 0·08 | 0·14 | −0·10 | 0·05 | 0·05 | 0·42 |
| Max R + Max S | AVG | 0·23 | 0·23 | 0·22 | 0·12 | 0·40 | 0·41 |
| | LVP | 0·12 | 0·24 | 0·07 | 0·01 | 0·22 | 0·58 |
| Mean$_d$ | AVG | 0·45 | 0·63 | 0·43 | 0·59 | 0·23 | 0·37 |
| | LVP | 0·52 | 0·66 | 0·63 | 0·75 | 0·44 | 0·19 |
| Mass | AVG | 0·36 | 0·50 | 0·41 | 0·51 | 0·29 | — |
| | LVP | 0·40 | 0·54 | 0·58 | 0·68 | 0·40 | — |
| Bennett[6] | AVG | 0·18 | 0·05 | 0·31 | 0·39 | 0·35 | 0·72 |
| | LVP | 0·16 | 0·005 | 0·34 | 0·39 | 0·35 | 0·68 |
| Aziz[7] | AVG | 0·35 | 0·58 | 0·33 | 0·60 | 0·12 | 0·48 |
| | LVP | 0·39 | 0·58 | 0·46 | 0·68 | 0·13 | 0·30 |

Mean$_d$, mean diastolic left ventricular wall thickness; AVG, aortic valve gradient, LVH, left ventricular hypertrophy; LVP, left ventricular pressure.



*Correlation of measured left ventricular pressure with three variables in 29 patients with high quality echocardiograms and good left ventricular function: (a) mean end diastolic left ventricular wall thickness (mean$_d$); (b) predicted left ventricular pressure as calculated from the formula of Bennett et al*[6]*; and (c) predicted left ventricular pressure as calculated from the formula of Aziz et al.*[7] *95% confidence intervals (95% CI) for standard error (SE) for the prediction of left ventricular pressures measured at catheterisation are shown.*

voltage criteria and ST depression. Sensitivity was fair but specificity poor for the voltage criteria. Sensitivity was similar and specificity greater with ST depressions, giving an overall accuracy that was 5–8% more than by voltage criteria. Correlation coefficients relating precordial voltages to pressure gradient across the aortic valve and left ventricular pressure were low (Table 2).

### PREDICTION OF SEVERITY OF AORTIC STENOSIS BY ECHOCARDIOGRAPHY

#### *Left ventricular wall thickness*

Correlations were determined between left ventricular pressure or pressure gradient across the aortic valve and septal thickness, left ventricular posterior wall thickness, and mean left ventricular wall thickness at end systole and end diastole. In general end diastolic measurements correlated better with the haemodynamic variables than end systolic measurements, and mean wall thickness correlated better than either septal or posterior wall thickness alone. In the group as a whole (group 1) left ventricular wall thickness predicted the severity of stenosis better than precordial electrocardiographic voltages. The highest correlation coefficient was found when 29 patients with good quality echocardiograms and mean Vcf >1 circ/s were selected (group 4) and the relation between mean diastolic wall thickness and left ventricular pressure was examined ($r=0·75$) (Table 2, Fig. a).

Sensitivity and specificity were calculated based on the premise that a mean left ventricular wall thickness >1·15 cm at end diastole indicated important ventricular hypertrophy (all echocardiographic measurements were made to the nearest 0·1 cm, but the process of calculating means produced figures with two places of decimals). For group 4 this gave a sensitivity of 89%, specificity of 73%, and accuracy of 83% for the prediction of pressure gradient across the aortic valve, the highest values for any of the methods used in this study. When the fair quality echocardiograms of patients with a mean rate of circumferential shortening $>1$ circ/s were analysed separately (group 5) correlations with left ventricular pressure and pressure gradient across the aortic valve were poor and resembled correlations with precordial electrocardiographic voltage. Even with the high quality echocardiograms, 95% confidence intervals for predicing left ventricular pressure from mean diastolic wall thickness were wide (Fig. a)—with a mean wall thickness of 1·15 cm predicting a left ventricular pressure of between 130 and 230 mm Hg. A mean wall thickness of 1·75 cm or greater was highly likely to be associated with a left ventricular pressure of greater than 180 mm Hg.

*Left ventricular mass*

The pattern of correlation coefficients for left ventricular mass was qualitatively similar to that with wall thickness, but less close (Table 2).

*Predicted left ventricular pressure*

Neither of the two formulas for predicting left ventricular pressure was as closely correlated with measured left ventricular pressure as was mean diastolic wall thickness, and 95% confidence intervals were wider (Table 2, Fig. b). Again, end diastolic measurements (as used in the formula of Aziz) were better predictors than end systolic measurements (as used in the formula of Bennett).

When a group (group 6) of children ($<16$ years) was analysed, the results were completely different (Table 2). The correlation of pressure gradient across the aortic valve or left ventricular pressure with mean diastolic wall thickness was poor, presumably because of the wide range of ages and therefore heart sizes in the group. The formulas for predicting left ventricular pressure, particularly the Bennett formula, were considerably more accurate.

## Discussion

The electrocardiographic[9-11] and echocardiographic[12] methods of demonstrating left ventricular hypertrophy have been separately evaluated in several studies, but the strengths and weaknesses of the methods cannot be demonstrated except by comparing them within the same group of patients. In one study in which this has been done it was concluded that precordial voltages were more accurate in predicting the severity of aortic stenosis than was echocardiographic measurement of left ventricular hyertrophy.[13] The criteria for diagnosing left ventricular hypertrophy by echocardiogram were not stated, however, and the quality of the echocardiograms was not assessed.

One of the strengths of electrocardiography is that it can be performed on all patients and there are no important technical constraints in making a recording. With echocardiography the technical quality of the recording is of great importance, particularly when thicknesses are measured, since even small errors are a considerable proportion of the total measurement.[14] In this study high standards were achieved in 42% of patients. When poorer quality echocardiograms were analysed, the correlations with pressure gradient across the aortic valve and left ventricular pressure were reduced to those achieved by electrocardiogram. When high quality echocardiograms were available, mean diastolic left ventricular wall thickness was the best predictor of the severity of aortic stenosis. In children wall thickness was a poor predictor of aortic stenosis because the range of heart sizes was much greater than that in adults. Precordial voltage, however, was if anything more accurate when applied to children than when applied to adults.

### HYPERTENSION

Hypertension is a potentially confounding variable in the relation between left ventricular wall thickness and pressure gradient across the aortic valve. Patients with established hypertension were excluded from the study, and no patients were on hypotensive treatment (even for angina). On admission to hospital five patients had a diastolic blood pressure of $>100$ mm Hg, but none was $>110$ mm Hg. Their mean (SD) systolic blood pressure was 158 (13) mm Hg. Because hypertension had not previously been recognised in these patients they were included in the study. Only two satisfied the criteria for group 4 (mean rate of circumferential shortening $>1$ circ/s and high quality echocardiograms).

### FORMULAS FOR PREDICTING LEFT VENTRICULAR PRESSURE

The theoretical basis for predicting left ventricular pressure is a highly simplified form of the law of Laplace, which states that circumferential stress in a thin-walled sphere is proportional to internal pressure and cavity diameter and inversely proportional to wall thickness. With several major assumptions this may be applied to the left ventricle.[15] On the basis that the hypertrophic response acts to keep peak circumferential wall stress constant in pressure overload (at least until the left ventricle fails[16]), left ventricular pressure is proportional to the ratio of left ventricular wall thickness to cavity dimension. Bennett *et al* were the first to realise the potential of this relation to predict left ventricular pressure by non-invasive means.[6] A number of similar formulas have since been devised[7 17-21] and have been shown to predict left ventricular pressure with some accuracy, although there have been reservations.[22 23] The formula of Aziz *et al*[7] was claimed to be superior because it used end diastolic measurements (rather than the end systolic measurements of Bennett's formula), since peak systolic wall stress occurs at the onset of systole before there has been appreciable fibre shortening.

Whatever the theoretical basis for the formulas, they all contain the well documented relation between left ventricular pressure and wall thickness, and for practical purposes it is important to know how much the formulas depends on this relation for their correlation, and how much the inclusion of the second variable, cavity dimension, alters the correlation. In the present study it was quite clear that except in children the correlation between left ventricular pressure and ventricular wall thickness was closer than the correlation between measured and predicted left ventricular pressures from the two formulas whatever group of adult patients was chosen. Left ventricular wall thickness was a poor predictor of left ventricular pressure in children, however, presumably because of the large range of heart sizes, and in children the Bennett formula performed reasonably well ($r=0{\cdot}68$). There is a close relation between cavity dimension and body surface area in children, even in those with aortic stenosis,[7] and the most likely explanation of these findings is that cavity dimension functions as a normalising variable and therefore is of most value in children where the range of cavity dimensions is largest. Although sensitivity was very low for the Aziz formula, specificity was high (93%). This was largely due to the fact that the formula tended to underestimate left ventricular pressure, particularly at the lower end of the pressure range as is shown by the regression line (Fig. c).

There are several other possible reasons why the formulas for predicting left ventricular pressure from echocardiographic recordings are inaccurate.

### *Poor quality of echocardiographic recordings*

Poor images cannot provide accurate measurements, and it is clear that the quality of echocardiographic recording is highly important. Poor image quality does not, however, explain why in the present study left ventricular wall thickness was a better predictor of left ventricular pressure than the two formulas since the same echocardiograms were used for determining both sets of correlations.

### *Inaccuracies of measurement*

Small inaccuracies of measurement are inevitable even in good quality echocardiograms,[24] although making repeated measurements minimises the errors.[14] In the calculation of a ratio such as $LVW_d/D_d$, however, inaccuracies tend to be amplified because an error in locating either endocardial boundary will increase one measurement and decrease the other. An error of as little as 1 mm in either endocardial boundary may change the predicted left ventricular pressure by as much as 20 mm Hg.

### *Assumptions in the derivation of peak circumferential wall stress*

The estimation of peak circumferential wall stress by M mode echocardiography requires the assumption that the left ventricle behaves as a thin walled sphere. If this assumption is only partly correct then the accuracy with which left ventricular pressure can be predicted by M mode echocardiography will be limited, even with a technically perfect recording.

### *Constancy of wall stress in aortic stenosis*

There is now a considerable body of experience suggesting that the process of adaptation to increase afterload is stimulated by abnormal wall stress and completed only when wall stress is returned to normal.[16 25] There have, however, been two reports of abnormal wall stress in patients with compensated aortic stenosis.[26 27]

The results of this study allow a clearer understanding of the place of these various methods of assessing left ventricular hypertrophy in the investigation of patients suspected of having important aortic stenosis. Of course in the clinical setting none of these variables would be used alone for the assessment of an individual patient, but a knowledge of the sensitivity, specificity, and confidence intervals indicates how much weight to place on a particular result. In adults, who are good echocardiographic subjects, mean diastolic wall thickness provides more reliable information than either the electrocardiogram or left ventricular pressure predicted from formulas. If the echocardiograms are anything less than high quality their reliability resembles that of the electrocardiogram. In children left ventricular pressure predicted from the echocardiogram is the most accurate method, but the correlations are not sufficiently strong for an investigator to be confident in borderline cases.

I am grateful to Graham Leech for his criticism of this paper.

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# Computer assisted echocardiographic assessment of left ventricular function before and after anatomical correction of transposition of the great arteries

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SUMMARY Left ventricular function before and after anatomical correction of transposition of the great arteries was assessed by computer assisted analysis of 78 echocardiographs from 27 patients obtained one year before to five years after operation. Sixteen patients had simple transposition, and 11 had complex transposition with additional large ventricular septal defect. Immediately after correction mean shortening fraction fell from 46 (9)% to 33 (8)%. There was a corresponding drop in normalised peak shortening rate from 5·4 (3·7) to 3·3 (1·1) $s^{-1}$ and normal septal motion was usually absent. Systolic shortening fraction increased with time after correction and left ventricular end diastolic diameter increased appropriately for age. The preoperative rate of free wall thickening was significantly higher in simple (5·6 (2·8) $s^{-1}$) and complex transposition (4·5 (1·8) $s^{-1}$) than in controls (2·9 (0·8) $s^{-1}$). After operation these values remained high in both the short and long term. Thus, computer assisted analysis of left ventricular dimensions and their rates of change before and after anatomical correction showed only slight postoperative changes which tended to become normal with time. Septal motion was commonly absent after operation. This was associated with an increase in the rate of posterior wall thickening that suggested normal ventricular function associated with an altered contraction pattern.

Computer assisted echocardiographic analysis may be helpful in the long term assessment of ventricular function after operation for various heart abnormalities.

When compared with intra-atrial procedures[1 2] for transposition of the great arteries, anatomical correction offers the potential advantage of converting the left ventricle to a systemic pump.[3] There are few data on left ventricular function immediately after or long after anatomical repair, and a safe, repeatable, preferably non-invasive, method of assessment is required. Computer assisted echocardiographic analysis is a sensitive reliable method of assessing ventricular function in both children[4] and adults,[5] and we have used it to evaluate patients before and after anatomical correction of transposition of the great arteries.

## Patients and methods

### STUDY GROUPS

We studied 27 patients who underwent anatomical correction of transposition of the great arteries. These children comprise 75% of all those who underwent this procedure at Harefield Hospital from October 1976 to January 1982. Most of the remaining children live abroad and were unavailable for re-examination. There was no other known bias in patient selection. Sixteen children (59%) had simple transposition without other important defects and 11 (41%) had additional lesions—a ventricular septal defect in 10 and an aortopulmonary window in one. All patients with simple transposition underwent either pulmonary artery banding or pulmonary artery banding combined with a Blalock-Taussig shunt[6] from 12 to 2·5 months before anatomical cor-

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Accepted for publication 14 September 1985

rection. Age at definitive repair ranged from 1 to 120 months (mean 14·6 months). Operative technique and perioperative management have been reported elsewhere.[7]

Preoperative echocardiograms were recorded from eight months to one day before anatomical correction, early postoperative echocardiograms from one day to six months after repair, and late postoperative studies from six months to five years after repair.

The control population consisted of 36 healthy children aged 18 to 97 months (mean 71·8). Some of these data have been reported in a previous paper.[4]

### M MODE ECHOCARDIOGRAMS

Echocardiograms were obtained in the standard manner[8] with a Smith-Kline Echoline machine interfaced with a Cambridge 70-A Multichannel recorder. An appropriate transducer was used with the patients in supine or left lateral position. Paper speed was usually 75 mm per second and a simultaneous electrocardiogram was always recorded. The transverse dimension of the left ventricle was always measured at the level of the mitral valve tips. An echocardiogram was acceptable for inclusion in the study when the right and left septal surfaces, left ventricular free wall endocardium, and left ventricular free wall epicardium were simultaneously displayed. The leading edge of each structure was traced in at least two and usually in five beats and the results were averaged. No premature or post-extrasystolic beats were included. There were 78 acceptable echocardiograms among 232 that were performed. Most of the original echocardiograms were unacceptable for digitisation because all four surfaces were not simultaneously imaged.

### DIGITISATION

Tracings were digitised by the method of Gibson and Brown.[9] End diastolic dimension was measured synchronously with the electrocardiographic Q wave. End systolic dimension was measured at the time of peak anterior motion of the posterior wall endocardium. This method differs from that recommended by the American Society of Echocardiography[10] because a method based on maximum posterior septal motion is inapplicable in a population with abnormal septal motion.

We analysed plots of left ventricular dimension, rates of change of dimension, normalised rates of change of dimension, as well as posterior wall and septal thickness and the rate of change of the thickness of the posterior wall (Fig. 1). From these measurements we obtained peak rates of change of dimension and wall thickness in both systole and diastole.

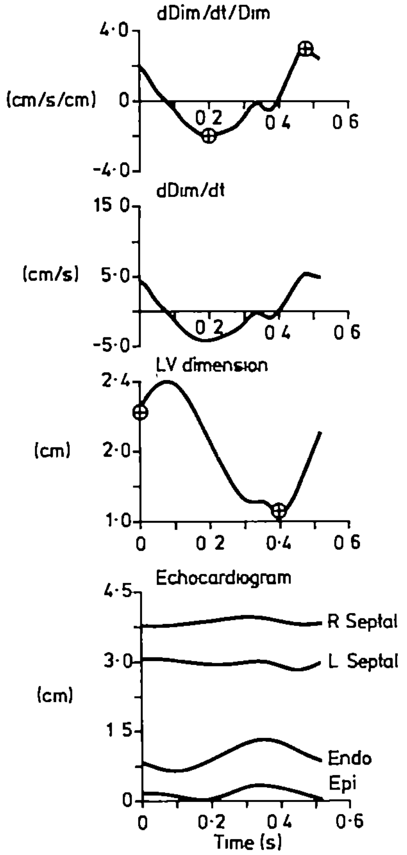

Fig. 1 *Typical computer printout of digitised beat showing echocardiogram, continuous left ventricular (LV) dimension with time, change in dimension with change in time, normalised change in dimension with change in time. Peak normalised rate of emptying and rate of filling are indicated by* ⊕.

### STATISTICAL ANALYSIS

Data were compared as individual data points as well as means (1 SD). We used a non-paired $t$ test for comparision between groups. A p value $<0·05$ was regarded as significant.

## Results

### LEFT VENTRICULAR END DIASTOLIC DIMENSION

Preoperative end diastolic dimension was smaller in patients with simple transposition (1·9 (0·4) cm) than in those with complex transposition (3·0 (0·4) cm) ($p<0·01$) (Fig. 2). Measurements from short term postoperative studies were not significantly different in simple and complex transposition. The mean left end diastolic dimension was 2·3 (0·8) cm in simple

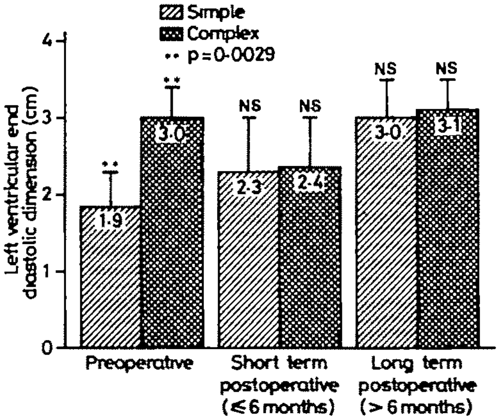

Fig. 2 *Left ventricular end diastolic dimension (LVEDD) before and after correction of transposition. Preoperative LVEDD was significantly greater in children with complex transposition. Postoperative values were not significantly different in either short or long term follow up.*

transposition and 2·4 (0·6) cm in complex transposition. Similarly there was no significant difference between the groups more than six months after repair—simple transposition 3·0 (0·6) cm and complex transposition 3·1 (0·5) cm. After anatomical correction there was growth of the left ventricle with time in all patients (Fig. 3).

SHORTENING FRACTION

The preoperative shortening fraction was higher in patients with simple transposition (51 (19)%) than in those with complex transposition (43 (7)%), but not significantly (Fig. 4). The shortening fraction before operation in both groups was significantly higher than in the controls (34(5)%) (p=0·0001 for simple transposition and p=0·007 for complex transposition).

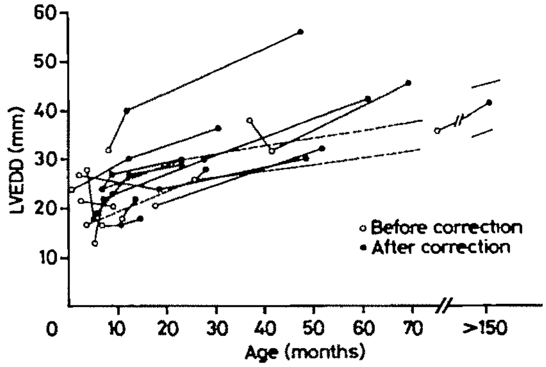

Fig. 3 *Left ventricular end diastolic dimension (LVEDD) (mm) in 14 patients in relation to age in months. 95% confidence limits of the line of regression are shown.*[11]

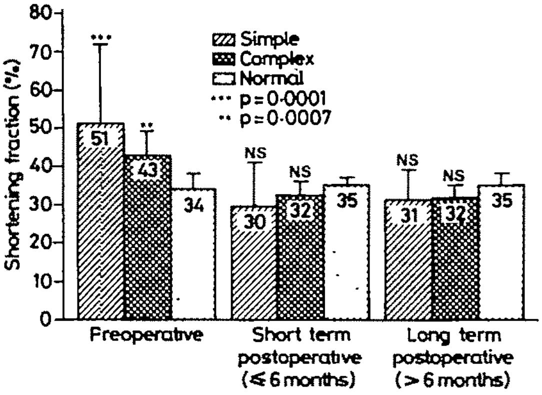

Fig. 4 *Shortening fraction before and after repair. The shortening fraction before operation was significantly higher in patients with simple and complex transposition than in controls. After operation there was a decrease in shortening fraction and postoperative values are not significantly different from that in controls.*

The shortening fraction fell immediately after operation to 30 (11)% in simple and 32 (4)%) in complex transposition. Neither value was signficantly different from that in controls (35 (2)%). In the long term the shortening fraction remained virtually unchanged (31 (8)% in simple transposition and 32 (4)% in complex tranpositions). Neither value was significantly different from that in controls (35 (3)%).

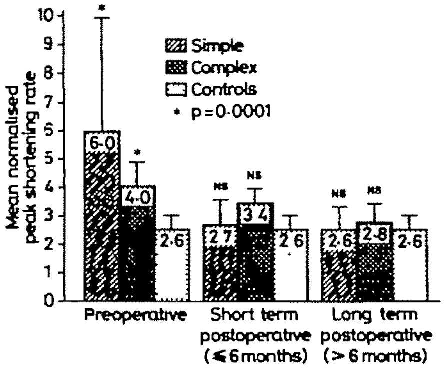

Fig. 5 *Normalised peak rate of shortening before and after repair. Before operation patients with simple or complex transposition had significantly greater normalised peak shortening rates than controls. After operation the normalised peak rate of shortening was not significantly different from that in controls.*

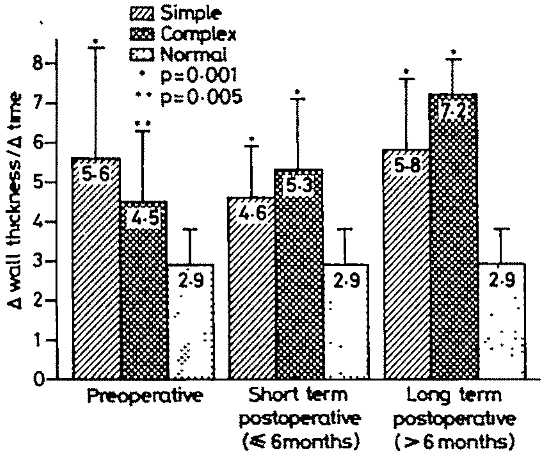

Fig. 6 *Free wall thickening before and after operation. At all stages the transposition groups have significantly higher rates of free wall thickening than the controls These differences tend to increase with time.*

NORMALISED PEAK RATES OF SHORTENING

Before operation peak normalised rates of shortening in patients with both simple and complex transposition were significantly greater than that in controls: 6·0 (3·9) $s^{-1}$ in simple and 4·0 (0·9) $s^{-1}$ in complex and 2·6 (0·5) $s^{-1}$ in controls (for both simple and complex p=0·0001) (Fig. 5). In the short term postoperative period both patient groups had reduced peak shortening rates (2·7 (0·9) $s^{-1}$ in simple and 3·4 (0·5) $s^{-1}$ in complex transposition). They were not significantly different from the rate in controls. Postoperative values in the long term were essentially unchanged (2·6 (0·8) $s^{-1}$ simple and 2·8 (0·5) $s^{-1}$ complex) and they were not significantly different from that in controls (2·6 (0·5) $s^{-1}$).

FREE WALL THICKENING

The postoperative rate of free wall thickening was significantly greater in patients with transposition than in controls (Fig. 6). These differences tended to increase with time after operation. The mean values for peak thickening rate before operation were 5·6 (2·8) $s^{-1}$ in simple transposition and 4·5 (1·8) $s^{-1}$ in complex transposition. They were significantly greater than that in controls (p=0·001 simple), (p=0·005 complex). These differences persisted in both groups soon after operation (simple 4·6 (1·2) $s^{-1}$, complex 5·3 (1·8) $s^{-1}$); controls 2·9 (0·8) $s^{-1}$ (p=0·001 for both comparisons). In the long term postoperative values in both patient groups remained raised (5·8 (1·7) $s^{-1}$ for simple transposition, 7·2 (1·0) $s^{-1}$ for complex tranposition, and 2·9 (0·8) $s^{-1}$ for controls) (p=0·001 for both simple and complex). These values were not significantly different from the immediate postoperative values. Patients with high values in the short term tended to have increased rate of free wall thickening in the long term studies as well (p=0·042).

SEPTAL MOTION

Septal motion was satisfactorily displayed in 23 patients before anatomical correction. It was normal in 21 (93%), absent in one (4%), and reversed in one (4%). Shortly after operation only four (17%) of 24 patients had normal septal motion. It was absent in 14 (58%) patients and reversed in six (25%). More than six months after anatomical correction 12 (48%) of 25 children had absent septal motion, while in five (20%) of 25 the direction was normal but amplitude was reduced. In eight (32%) of 25 normal direction and amplitude of septal motion had returned.

## Discussion

After Mustard[1] and Senning[2] procedures both clinical and subclinical systemic (right) ventricular dysfunction are known to occur.[12–14] The major potential advantage of anatomical correction of transposition of the great arteries is the conversion of the left ventricle to a systemic pump. The long term success of anatomical correction is, therefore, dependent on adequate left ventricular function. It is not clear if completely normal function can be expected. Even after repair of relatively simple lesions, such as isolated ventricular septal defect, left ventricular dysfunction has been reported.[15,16] Newer operative techniques and early surgical repair, however, seem to have improved postoperative ventricular size and function.[17] Transient left ventricular failure has been reported immediately after anatomical correction of transposition of the great arteries.[18,19] In long term survivors, however, left ventricular ejection fraction and end diastolic pressure are reported to be normal.[20] The left ventricular contractile state was examined after operation in a small series of children from Harefield. In every child who underwent repair before the age of one the left ventricular end diastolic dimension and wall stress-shortening were normal.[21]

Echocardiographic findings have been described before and after arterial switch[22] and Mustard procedure in children for transposition of the great arteries.[23] Septal motion was judged to be abnormal in almost all children before and after Mustard's operation.[23] When anatomical correction or the arterial switch included repair of a ventricular septal defect, septal motion was always abnormal.[22] After an intra-atrial repair, septal motion may be incorporated into emptying of the high pressure right ventricle. Absent or paradoxical septal motion is common after open heart procedures and should not be equated with intrinsic ventricular dysfunction.[24] In our current series only 4% of children had normal septal motion immediately after operation. More than six months after repair, however, 32% of the patients had normal septal motion.

Before operation the left ventricular dimension was larger when a ventricular septal defect was present (Fig. 2). This is probably the result of shunting from the systemic right ventricle to the pulmonary left ventricle. In a group studied in Toronto left ventricular size vaired considerably before definitive correction.[22]

In our series, there were no significant differences in left ventricular size between patients with simple transposition or those with complex transposition, either immediately or more than six months after operation. In addition left ventricular size increased appropriately with advancing age (Fig. 4). We know of no other series in which the growth of the left ventricle has been evaluated after anatomical correction.

Before repair the shortening fraction was higher than normal in both those with simple and those with complex transposition (Fig. 5). Despite adequate pulmonary artery banding in patients with simple transposition, the left ventricular afterload is probably subsystemic. This may account for the increased shortening fraction. The increased normalised peak shortening rates in the patients before operation could also be explained by reduced left ventricular afterload.

After repair there was a signficant reduction in shortening fraction, but values in those with simple and those with complex transposition were not significantly different from that in controls. Peak shortening rates also fell to normal values immediately after repair and remained normal in long term studies.

Rates of free wall thickening in those with simple and those with complex transposition were significantly greater than normal (Fig. 6). In the preoperative period this increased rate of thickening could be explained on the basis of diminished afterload; that is the left ventricular free wall contracts faster in the face of low afterload. In both short and long term postoperative follow up studies the rate of free wall thickening remained greater than normal and may increase with time. In the presence of flat or diminished septal motion and normal peak rate of shortening, the rate of posterior wall thickening may increase as a compensatory response and produce a normal shortening fraction. There was a close correlation between an increase in the long term rate of free wall thickening and high shortening fraction ($p = 0{\cdot}028$).

These data indicate changes in ventricular wall motion both before and after anatomical correction. The reductions in shortening fraction, in the amplitude of septal motion, and in peak shortening rate in the immediate postoperative period are probably related to the sudden change in ventricular afterload and the effects of open heart surgery itself. Postoperative differences include reduced septal motion and persistence of the increase in rate of thickening of the posterior wall. This latter feature cannot be explained on the basis of overall movement of the heart in space but, taken in conjunction with septal hypokinesis, seems to indicate a pattern of contraction that is altered, but not necessarily impaired since changes in overall cavity size were normal and since the systemic ventricle grows with age. These data are part of a continuing study that may shed further light on this question. Although even more long term results are not yet available, observations as long as five years after correction seem to indicate adequate left ventricular function after correction. We conclude that left ventricular function is maintained after anatomical correction of transposition of the great arteries.We expect that this operation will become more widely accepted as the procedure of choice for selected infants.

We thank Karl Hammermeister for assistance with digitising, David Hughes and Steve Saunders for help with computer programming, and D Naftel, E Blackstone (of the University of Alabama), and Harry Davis for statistical assistance.

F W A was a British-American Research Fellow of the American Heart Association and British Heart Foundation.

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# Hypertrophic cardiomyopathy in three generations of a large Norwegian family

## *A clinical, echocardiographic, and genetic study*

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SUMMARY Hypertrophic cardiomyopathy is a heart muscle disease with an obscure aetiology. Data from four generations of a large family (71 members) are presented. The occurrence of hypertrophic cardiomyopathy among members of the two oldest generations was compatible with a pattern of autosomal dominant inheritance. Seven out of 14 siblings in the second generation had definite signs of or were clinically suspected of having hypertrophic cardiomyopathy. The severity and distribution of left ventricular hypertrophy varied, but three (21%) brothers in generation II showed the classic picture of left ventricular outflow obstruction. Four siblings (29%) died suddenly aged 11, 22, 38, and 40 years. A high incidence of the disease would have been expected in the two younger generations (41 members, aged 1–31 years), but only two, a 16 year old boy and a 17 year old girl had signs of asymmetric septal hypertrophy. Current diagnostic procedures, including M mode and cross sectional echocardiography, are not sufficiently sensitive to identify young family members who may have preclinical hypertrophic cardiomyopathy.

No evidence for close genetic linkage between a postulated locus for hypertrophic cardiomyopathy and the major histocompatibility complex (antigens HLA-A, HLA-B, and HLA-DR) was found.

Hypertrophic cardiomyopathy is a disease of unknown cause. Several studies, however, have shown that the disease is common in some families, and that in such families hypertrophic cardiomyopathy may be transmitted as an autosomal dominant trait.[1–4] An association between the trait and human leucocyte antigen HLA-DRW4 has been reported in Japanese families,[5] and Kishimoto *et al* have suggested that there may be two separate forms of the disease—a familial form linked to the HLA complex, and a non-linked sporadic type.[6] In a study of 50 unrelated white North Americans with hypertrophic cardiomyopathy, however, Gardin *et al* did not find HLA-A, HLA-B, or HLA-C locus antigens useful as markers for this disease.[7] Recent studies by Maron *et al* suggested the possibility of a pattern of autosomal dominant inheritance of hypertrophic cardiomyopathy in only 30 of 70 families.[8] Maron *et al* also proposed that the wide range of phenotypic expressions observed may be due to genetic as well as to non-genetic causes. Genetic studies on hypertrophic cardiomyopathy have generally been carried out on rather small families, or on different families grouped together. In the present study we report the clinical, echocardiographic, and HLA findings in a large family through four generations. We studied the spectrum of phenotypic manifestations of a postulated single hypertrophic cardiomyopathy gene inherited as an autosomal dominant trait in this family. We also studied whether hypertrophic cardiomyopathy cosegregated with a particular HLA haplotype in this family. In that case, this HLA haplotype could be a presymptomatic predictor of the disease and might enable early medical intervention.

## Patients and methods

The family studied consisted of four generations

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Accepted for publication 22 July 1985

comprising a total of 71 members (Fig. 1). Physical and echocardiographic examinations were performed on all except two family members (III-6, III-8). In addition, a 12 lead electrocardiogram and chest *x* ray films were taken on members of generations I, II, and III. M mode and cross sectional echocardiography were performed with an IREX III, phased array, ultrasonic scanner with a 2·4 MHz handheld transducer. M mode echocardiograms were recorded by means of a heat processed black and white strip chart recorder at a paper speed of 50 mm/s. The cross sectional echocardiographic examinations of the youngest individuals were performed with a Toshiba SAL 50 linear array ultrasonic scanner with a 5 MHz transducer. The thickness of the ventricular wall was measured from the leading edges of the echoes with the transducer being held perpendicular to the chest wall in the standard position.[9] The diagnostic criterion of hypertrophic cardiomyopathy or asymmetric septal hypertrophy in adults was increased thickness of the interventricular septum with a septum:posterior left ventricular wall ratio $> 1{\cdot}4$ in the absence of cardiac or systemic disease capable of producing left ventricular hypertrophy. A septum:posterior left ventricular wall ratio equal to 1·4 was regarded as normal in individuals aged $> 20$ years, but as indicating hypertrophic cardiomyopathy in individuals aged $\leqslant 20$ years. In children the criterion of abnormal septal thickness was a measurement exceeding the age specific 95% confidence interval.[10]

The HLA antigens were determined by lymphocytotoxicity tests as previously described,[11] with highly selected antisera defining 13 antigens of the HLA-A series, 22 of the HLA-B series, and 8 of the HLA-DR series. On the basis of the results of the

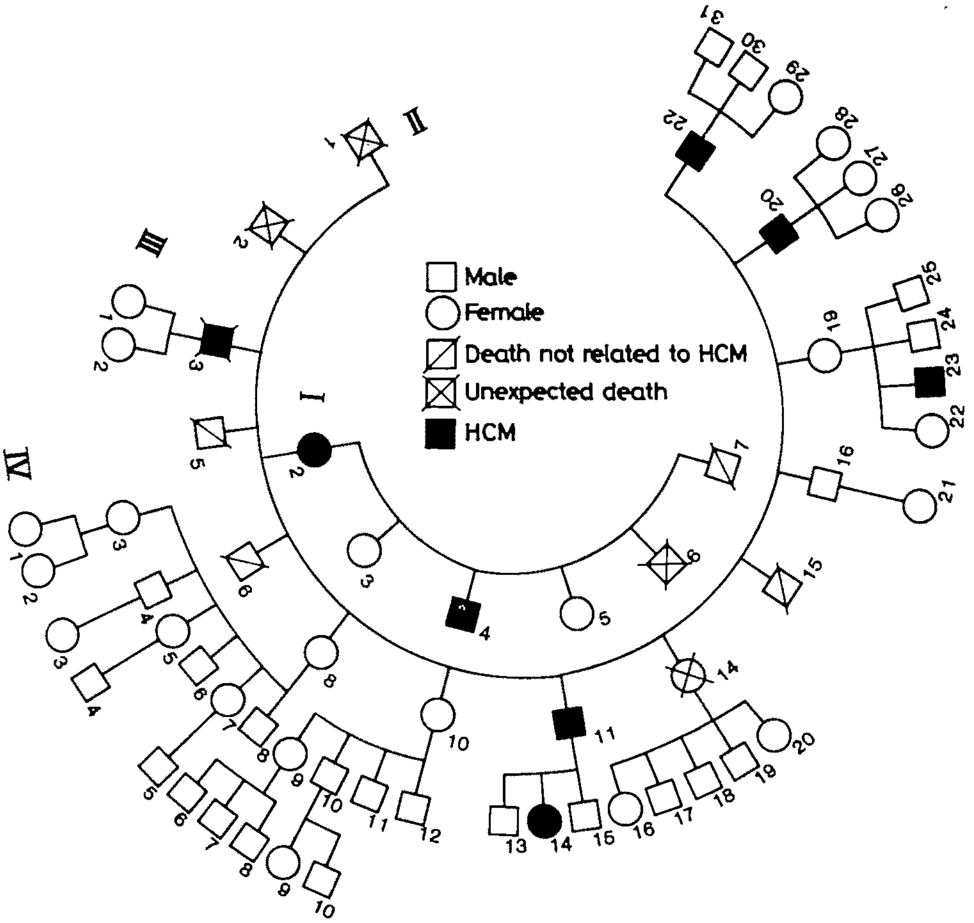

Fig. 1 *Pedigree of the family. Roman numerals refer to generations. Each family member has an index number. HCM, hypertrophic cardiomyopathy.*

family typing, the HLA haplotypes could be deduced in some members of the family who were dead. An HLA haplotype is defined as the genetic information in HLA antigens carried by the HLA-complex on each of the two chromosomes of pair number 6.

## Results

The results obtained in the four different generations are presented in chronological order. Selected data are summarised in Table 1.

### GENERATION I

The proband was a 74 year old woman (I-2). At the time of this investigation she had symptoms of heart failure and was in functional class II (New York Heart Association). On cardiac auscultation she had an apical systolic murmur grade 2/6 and her electrocardiogram showed atrial fibrillation and ST segment elevation in precordial leads V2–V4. A chest *x* ray film showed an enlarged heart with a total volume of 1400 ml (normal volume 830 ml/m$^2$). An echocardiogram showed a dilated left atrium (diameter 70 mm) and thickening of the interventricular septum (17 mm). The septum:posterior left ventricular wall ratio was 2·1. There was no systolic anterior movement of the mitral valve, but the septum showed decreased thickening fraction. Her husband (I-1) had died of myocardial infarction before the start of this study.

Her sister (I-3) had a 30 year history of cardiac failure, and had been treated with digoxin and diuretics. She had a grade 1/6 systolic heart murmur and her electrocardiogram showed left bundle branch block. The echocardiogram showed a dilated left ventricle with general hypokinesia. There were no valve abnormalities and she had no symptoms of angina pectoris. The findings in I-3 were compatible with congestive cardiomyopathy.

I-4 had no symptoms of cardiac disease at the time of study. He had a grade 1/6 systolic heart murmur and an electrocardiogram showed right bundle branch block. An echocardiogram showed increased thickness of the anterolateral wall of the left ventricle. There was no evidence of left ventricular outflow obstruction. I-4 has three children (not shown on the pedigree). His daughter aged 29 years had no symptoms or signs of cardiac disease. His son aged 27 years had no symptoms of heart disease, but the echocardiogram showed asymmetric septal hypertrophy with a septum:posterior left ventricular wall ratio of 1·5. His youngest son aged 26 years had normal left ventricular dimensions, but the electrocardiogram showed frequent ventricular extrasystoles and episodes of ventricular bigeminy. I-5 had a 15 year history of hypertension. She had no symptoms or signs of cardiomyopathy. I-6 died suddenly at the age of 45 years while performing moderate physical exercise. He had had no symptoms of severe illness. He had five children (not shown on the pedigree) and three were examined. A son aged 31 years had echocardiographic signs of hypertrophic cardiomyopathy, with a septal thickness of 15 mm, while two younger daughters had no evidence of cardiac disease. I-7 died at the age of 36 years from cancer.

### GENERATION II

The proband (I-2) has had 14 children of whom seven had died by the time this investigation was started. One (II-5) was stillborn, and two died when very young; II-6 had a fatal accident, and II-15 died from pneumonia. Two brothers (II-1 and II-2) died suddenly at the ages of 22 and 11 years. They had had no symptoms of severe disease. II-3 was

Table 1 *Clinical, electrocardiographic, and echocardiographic findings*

| *Generation* | *Pedigree No, sex, and age (yr)* | | | *Symptoms* | *Electrocardiogram* | *Echocardiographic data* | | | *Status* |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | *IVS (mm)* | *IVS/PW* | *SAM* | |
| I | 2 | F | 74 | Heart failure | AF, ST elevation V2-V4, | 17 | 2·1 | 0 | Alive |
| | 4 | M | 56 | 0 | RBBB, LAD | 16 | 1·8 | 0 | Alive |
| II | 3 | M | 38 | AP | LVH, LVS | NA | NA | NA | Dead |
| | 11 | M | 46 | AP | AVB I, LVH, LVS | 25 | 2·8 | + | Alive |
| | 19 | F | 40 | 0 | T neg V3, V4; isoelectric V5, V6 | 10 | 1·4 | 0 | Alive |
| | 20 | M | 38 | AP | QI, aVL; non-specific ST changes V3-V5 | 33 | 3·3 | + | Alive |
| | 22 | M | 34 | 0 | QII, III, aVF, T neg I, aVL, V3, V4; RBBB | 14 | 1·8 | 0 | Alive |
| III | 23 | M | 16 | 0 | 0 | 13 | 1·6 | 0 | Alive |
| | 24 | M | 11 | 0 | T neg V3 | 4 | 1·0 | 0 | Alive |

AF, atrial fibrillation; AP, angina pectoris; AVB I, atrioventricular block grade I, IVS interventricular septum; LAD, left axis deviation; LVH, left ventricular hypertrophy; LVS, left ventricular strain; PW, posterior left ventricular wall; RBBB, right bundle branch block; SAM, systolic anterior movement of mitral valve, +, present; 0, absent; NA, not available.

referred to hospital in 1967 at the age of 31 years. He had disabling symptoms of angina pectoris and clinical examination showed findings typical of hypertrophic cardiomyopathy with an apical systolic ejection murmur grade 4/6. Haemodynamic and angiographic studies confirmed the diagnosis. There was a peak systolic left ventricular outflow gradient of 65 mm Hg at rest which was reduced to 20 mm Hg after an oral dose of 40 mg propranolol. He was treated with propranolol, but died suddenly seven years later at the age of 38 years.

II-11 was admitted to hospital at the age of 40 years. He had a 15 year history of angina pectoris. Clinical examination showed a systolic ejection murmur grade 3/6. Echocardiography showed asymmetric septal hypertrophy (Fig. 2) and this was verified on cardiac catheterisation. A peak systolic subvalvar aortic gradient at rest of 56 mm Hg was reduced to 24 mm Hg after 8 mg of intravenous propranolol. Five years later he developed atrial fibrillation which was successfully treated with direct current cardioversion. He is now being treated with amiodarone and a small dose of propranolol. II-14 died suddenly at the age of 40 years. She was known to have a systolic cardiac murmur, but no signs of severe disease. II-19 had no symptoms of heart disease, but the electrocardiogram showed T wave inversion in precordial leads V3 and V4 and an isoelectric T wave in V5 and V6. The interventricular septum was normal (10 mm) at end diastole and the septum:posterior left ventricular wall ratio was 1·4.

II-20 had a four year history of angina pectoris when he was admitted to hospital at the age of 37 years. He had an apical systolic murmur grade 4/6 and echocardiography showed systolic anterior movement of the mitral valve and thickening of the interventricular septum (Fig. 3). Haemodynamic studies showed a peak left ventricular outflow gradient in systole of 43 mm Hg which was reduced to 15 mm Hg after 4 mg of intravenous propranolol. He has since been treated with oral propranolol. II-22 had no symptoms of heart disease at the time of this investigation. Examination of the heart showed a systolic murmur grade 2/6. The electrocardiogram had abnormal Q waves in the inferior leads, T wave inversion in precordial leads, and evidence of right bundle branch block. The echocardiogram showed thickening of the interventricular septum (14 mm), and the septum:posterior left ventricular wall ratio was 1·8. There was no systolic anterior movement of the mitral valve and the increased septal thickness was most pronounced in the apical region. No family members with evidence of hypertrophic cardiomyopathy had essential hypertension, and the three members in whom cardiac catheterisation was performed had normal coronary angiograms. II-8, II-10, and II-16 had no symptoms or signs of hypertrophic cardiomyopathy. None of the nine spouses in generation II had symptoms or signs of cardiac disease.

### GENERATION III

Generation III consisted of 31 members. Their ages ranged from 1 to 31 years. None had clinical symptoms of cardiac disease. An echocardiogram of III-23, a boy aged 16, showed thickening of the interventricular septum (13 mm) and a septum:posterior left ventricular wall ratio of 1·6. There was no systolic anterior movement of the mitral valve and the electrocardiogram was normal. His brothers and sister had no clinical or echocardiographic signs of cardiac disease. Both III-4 and III-14 had a septum:posterior left ventricular wall ratio of 1·4 but no increased septal thickness. According to our definition III-14, a 17 year old girl, probably had hypertrophic cardiomyopathy. The spouses in this generation were not examined.

### GENERATION IV

Generation IV consisted of 10 apparently healthy young children. None of them had signs or symptoms of hypertrophic cardiomyopathy.

### SEARCH FOR GENETIC LINKAGE

HLA typing was restricted to members of generations I and II and to selected members of generation III. The HLA haplotypes of I-1 and II-3 could be deduced from typing their spouses and children. Table 2 summarises the results of the HLA typing. All definitely affected members in generations I and II carry the HLA haplotype A1 B37 DR7. Two apparently unaffected members (I-5 and II-16), however, also have this haplotype. The only family member of generation III (III-23) who both met the criteria for being classified as having hypertrophic cardiomyopathy and had HLA typing, has inherited the alternative HLA haplotype (A11 B7 DR2) from his maternal grandmother (I-2), who also had hypertrophic cardiomyopathy.

## Discussion

The frequency of hypertrophic cardiomyopathy was high in generations I and II. The severity and distribution of left ventricular hypertrophy varied, but members of generation II were most severely affected. In this generation, two living brothers (II-11 and II-20) and one brother who died suddenly (II-3) had definite signs of hypertrophic cardiomyopathy with pronounced left ventricular outflow obstruction. They presented clinically with symp-

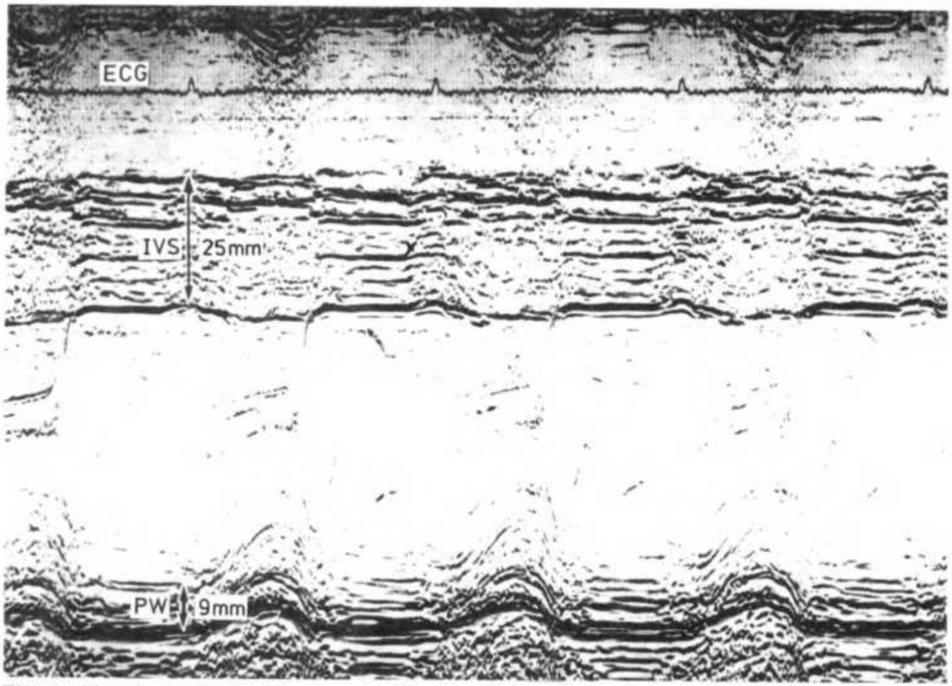

Fig. 2 *M mode echocardiogram of case II–11 with definite evidence of asymmetric septal hypertrophy. IVS, interventricular septum; PW, posterior left ventricular wall; ECG, electrocardiogram.*

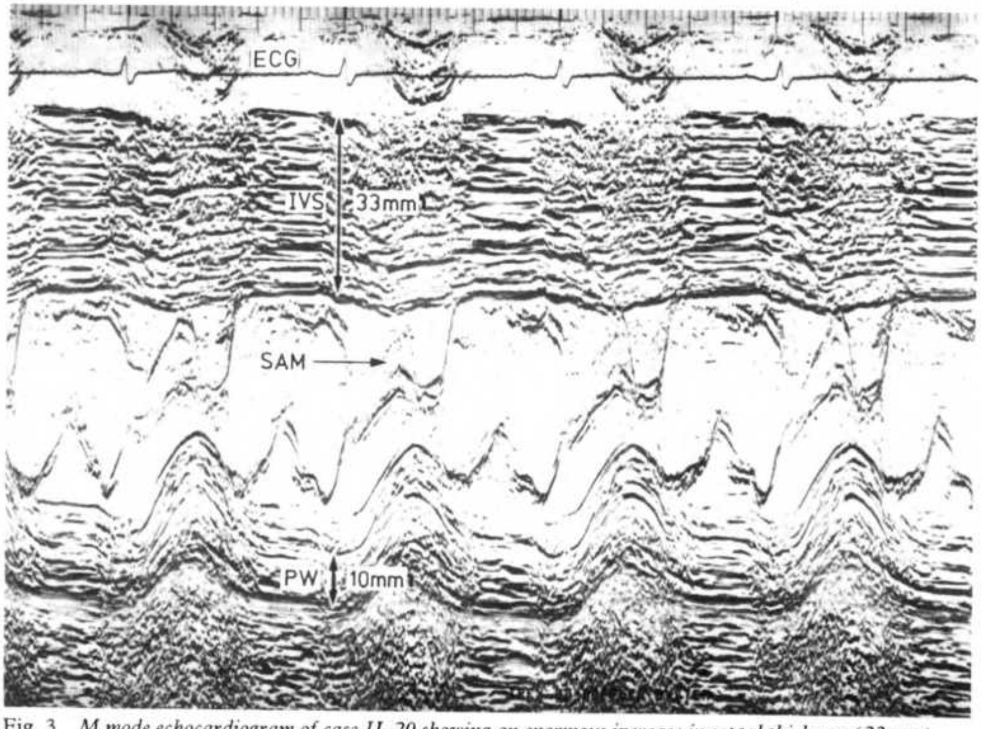

Fig. 3 *M mode echocardiogram of case II–20 showing an enormous increase in septal thickness (33 mm) and evidence of systolic anterior movement of the mitral valve (SAM, which indicates left ventricular outflow obstruction. IVS, interventricular septum; PW, posterior left ventricular wall; ECG, electrocardiogram.*

Table 2 *HLA histocompatibility markers in selected family members*

| *Generation* | *Pedigree No, sex, and age (yr)* | | | *HLA haplotypes* | | | *HCM* | *Genes coupled*† |
|---|---|---|---|---|---|---|---|---|
| I | 1 | M | 67 | A2 | B7 | DR4 | NA | Spouse |
| | | | | A19 | B18 | DR3* | | |
| | 2 | F | 74 | A11 | B7 | DR2 | + | Index |
| | | | | A1 | B37 | DR7 | | |
| | 3 | F | 60 | A11 | B7 | DR2 | 0 | Yes?‡ |
| | | | | A2 | B37 | DR7 | | |
| | 4 | M | 56 | A11 | B7 | DR2 | + | Yes |
| | | | | A1 | B37 | DR7 | | |
| | 5 | F | 52 | A11 | B7 | DR2 | 0 | No |
| | | | | A1 | B37 | DR7 | | |
| II | 3 | M | 38 | A2 | B7 | DR4 | + | Yes |
| | | | | A1 | B37 | DR7* | | |
| | 8 | F | 55 | A19 | B18 | DR3 | 0 | Yes |
| | | | | A11 | B7 | DR2 | | |
| | 10 | F | 52 | A19 | B18 | DR3 | 0 | Yes |
| | | | | A11 | B7 | DR2 | | |
| | 11 | M | 46 | A19 | B18 | DR3 | + | Yes |
| | | | | A1 | B37 | DR7 | | |
| | 16 | M | 42 | A19 | B18 | DR3 | 0 | No |
| | | | | A1 | B37 | DR7 | | |
| | 18 | M | 44 | A2 | B15 | DR4 | 0 | Spouse |
| | | | | A1 | B7 | DR4 | | |
| | 19 | F | 40 | A2 | B7 | DR4 | 0 | No§ |
| | | | | A11 | B7 | DR2 | | |
| | 20 | M | 38 | A2 | B7 | DR4 | + | Yes |
| | | | | A1 | B37 | DR7 | | |
| | 22 | M | 34 | A2 | B7 | DR4 | + | Yes |
| | | | | A1 | B37 | DR7 | | |
| III | 22 | F | 18 | A11 | B7 | DR2 | 0 | No?§ |
| | | | | A2 | B15 | DR4 | | |
| | 23 | M | 16 | A11 | B7 | DR2 | + | Yes§ |
| | | | | A2 | B15 | DR4 | | |
| | 24 | M | 11 | A1 | B7 | DR4 | 0 | NA§ |
| | | | | A2 | B7 | DR4 | | |

HCM, hypertrophic cardiomyopathy; +, present; 0, absent, NA, data not available, *haplotypes deduced from family typing

†Assumption: The gene locus for hypertrophic cardiomyopathy is located near the HLA complex on chromosome number 6. I-2 is used as an index person. "Yes" indicates either haplotype A1 B37 DR7 and hypertrophic cardiomyopathy, or A11 B7 DR2 and no disease. Observation of co-inheritance is compatible with, but does not prove, genes linkage (no recombination) "No" indicates either haplotype A11 B7 DR2 and hypertrophic cardiomyopathy, or A1 B37 DR7 and no disease. Observation indicates a crossover during sex cell formation in parent (recombination).

‡Insufficient information Haplotype A2 B37 DR7 may represent a third distinct haplotype in this sibship or be the product of a crossover within the HLA complex

§II-19 is healthy, but she has a son (III-23) with cardiomyopathy. II-19 must therefore have received the gene for hypertrophic cardiomyopathy with the A11 B7 DR2 haplotype from her affected mother I-2 (recombination), and transmitted both traits together to her son (non-recombination). Her daughter III-22 is too young to yield information, and III-24 has not inherited any of the HLA haplotypes from his maternal grandmother

toms of coronary heart disease. The youngest brother (II-22) had no symptoms of heart disease at the time of this study but the electrocardiogram was abnormal (Table 1) and the echocardiogram showed asymmetric septal hypertrophy without outflow obstruction.

There was also a high frequency of sudden unexpected deaths in the family. Two brothers (II-1 and II-2) died suddenly at the age of 22 and 11 years, respectively, one of them while playing in the schoolyard. Their sister (II-4) died suddenly at the age of 40 years. She had a systolic cardiac murmur but no symptoms of heart disease. In generation I, I-6 died suddenly at the age of 45 years, and an echocardiographic study of his son showed signs of hypertrophic cardiomyopathy. Sudden death is common in families with hypertrophic cardiomyopathy, probably as a result of ventricular arrhythmias or acute haemodynamic changes. It is likely that the three siblings in generation II and their uncle (I-6) died of a cardiac arrhythmia, and we assume that they all had hypertrophic cardiomyopathy. The distribution of affected family members in generations I and II is compatible with autosomal dominant inheritance. We examined the three children of I-4 and three of the five children of I-6. All were symptom free. In both sibships (not shown on the pedigree) a son with definite asymmetric septal hypertrophy was found. This father to son transmission of the trait excluded X linked inheritance but was consistent with the postulated autosomal dominant mode of inheritance.

Kishimoto *et al* suggested that a gene locus for hypertrophic cardiomyopathy may be located on chromosome number 6 within mapable distance of the HLA complex in some families.[6] Table 2 outlines the distribution of HLA haplotypes in some family members. Table 2 also indicates whether the two traits were inherited together as would have been expected if there were close genetic linkage. If the gene for hypertrophic cardiomyopathy is located on chromosome number 6, very close to the HLA complex, a particular HLA haplotype should consistently be found together with the gene for hypertrophic cardiomyopathy in a given family. The further apart on a chromosome two traits are located, the more frequently they will tend to separate during the formation of sex cells. Genes far apart on the same chromosome or situated on different chromosomes segregate independently and with equal frequency to the offspring.

In this family, eleven people may be informative (Table 2). Because the observed distribution (three recombinants, eight non-recombinants) or a more skewed distribution would occur by chance in 11·3% of such sets of observations this distribution may have arisen by chance. Thus, HLA typing in this family was not useful for the identification of presymptomatic gene carriers of hypertrophic cardiomyopathy. Loose genetic linkage between the two traits, however, cannot yet be excluded. In this family more information may be gained by extending the HLA typing to other family members (for example to III-14, descendants of I-3, I-4, I-5, and I-6) and by including in the analysis other genetic chromosome number 6 markers outside the HLA complex. The distribution of HLA haplotypes among the siblings of I-2 could then be clarified, and the assumed crossover events in the vicinity of the HLA complex on chromosome number 6 (sex cells from I-2 to II-16 and II-19) may be corroborated. Formal linkage analysis will be performed in this family when such information is available.

A high frequency of hypertrophic cardiomyopathy would be expected in generations III and IV, but only a 16 year old boy (III-23) and the 17 year old girl (III-14) showed evidence of asymmetric septal hypertrophy. This observation suggests that other factors in addition to a genetic predisposition may be necessary for clinical hypertrophic cardiomyopathy to develop. This accords with studies by Emanuel *et al* who have shown that clinical hypertrophic cardiomyopathy may not become evident until adolescence or even early adult life.[12] Thus, the development of septal hypertrophy may be age dependent. There is strong evidence that catecholamines can stimulate the growth of septal tissue and thereby accelerate the disease process. Data obtained by infusion of noradrenaline in dogs raise the possibility that the interventricular septum is more sensitive to beta adrenergic stimulation than either the right ventricle or the free wall of the left ventricle.[13] This suggests that increased sympathetic activity or increased sensitivity to catecholamines are possible mechanisms for the development of hypertrophic cardiomyopathy in the human heart. Studies by Yamori *et al* suggested that the beta adrenergic effects of noradrenaline were more potent than its alpha effects in inducing cardiac hypertrophy.[14] This may explain the beneficial haemodynamic effect of beta blockers in patients with hypertrophic cardiomyopathy. In the present family three brothers (II-3, II-11, II-20) in generation II had evidence of left ventricular outflow obstruction. They were all examined by cardiac catheterisation and there was a substantial reduction in the peak systolic gradient after administration of propranolol.

Echocardiography offers a unique method of diagnosing patients with established hypertrophic cardiomyopathy. The severity of myocardial disease may be assessed and future management guided. This method, however, has not been useful in identifying young patients at risk for developing this disease. In the present family, only three family members (II-22, III-14, and III-23) and the sons of I-4 and I-6 were diagnosed by echocardiography as having hypertrophic cardiomyopathy without clinical symptoms of cardiac disease. Because there is evidence for an autosomal dominant mode of inheritance of the disease in this family, we expect that many members of the two younger generations will develop signs of the disease as adults. Longitudinal echocardiographic studies combined with functional assessments may be of some value in increasing the diagnostic rate in these younger age groups. No other existing methods are likely to be more useful in the diagnostic evaluation of hypertrophic cardiomyopathy.

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# Conversion of paroxysmal atrial fibrillation to sinus rhythm by intravenous pirmenol

## *A placebo controlled study*

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SUMMARY The efficacy of pirmenol (a class I antiarrhythmic agent) as a converter of paroxysmal atrial fibrillation was investigated. Forty patients without congestive heart failure or a history of sinus node disorder were randomly allocated to receive either intravenous pirmenol (50–100 mg) or placebo in a double blind trial. In 12 of 20 patients sinus rhythm was restored 2–16 minutes after pirmenol, and in 3 of 20 patients in the control group it returned within one hour. A nodal escape rhythm was seen during sinus slowing in one patient, but in other patients there was no sinus arrest, atrioventricular conduction disturbance, or hypotension. The ventricular rate was slightly increased in patients in whom sinus rhythm was not restored by pirmenol. The results indicate that pirmenol has an antifibrillatory effect on the atria. Sinus rhythm was restored rapidly after intravenous administration. It was well tolerated in patients with atrial fibrillation of recent onset.

Pirmenol has class I antiarrhythmic effects in Purkinje fibres.[1] It suppresses premature ventricular complexes in patients[2 3] and terminates paroxysmal supraventricular tachycardia.[4] Depression of the fast inward current and a considerable increase in the duration of action potential in the rabbit atria have been reported,[5] which might suggest an antifibrillatory effect on the atria. Pirmenol converted atrial tachycardia and fibrillation to sinus rhythm in dogs.[6]

The present randomised double blind study was undertaken to examine the efficacy of intravenous pirmenol in the acute treatment of paroxysmal atrial fibrillation.

## Patients and methods

Forty patients admitted to a hospital emergency department with atrial fibrillation of recent onset (⩽48 hours) participated in the study. Patients known or suspected to have a sinus node or atrioventricular conduction disorder, acute myocardial infarction, or other severe illness, or congestive heart failure leading to interstitial extravasation shown by chest radiography were excluded. Patients who had taken digitalis or beta blocking agents ⩾3 hours before the study were included, but those patients on other antiarrhythmic agents were excluded. The appearance of symptoms was taken to indicate time of onset of fibrillation.

The patients were observed over 30 minutes for clinical evaluation and to allow their condition to stabilise. They were observed for 60 minutes after administration of pirmenol or placebo. A two lead electrocardiogram with a time track was continuously recorded at a paper speed of 50 mm/s for analysis of the rhythm, heart rate, and electrocardiographic intervals. Brachial cuff blood pressure was measured every five minutes. Patients were randomly allocated to receive either pirmenol or placebo (20 patients each) in a double blind trial. Pirmenol (a 50 mg bolus in 5 ml of physiological saline) or 5 ml of physiological saline were injected over 2 minutes and the dose was repeated after 10 minutes if sinus rhythm had not returned. Blood samples for the determination of plasma concentrations of pirmenol were drawn five minutes after the injections and at the end of the 60 minute observation period. Chest

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Accepted for publication 30 September 1985

radiographs and M mode echocardiography for determination of left atrial end systolic diameter and left ventricular dimensions according to European standards[7] were obtained when in sinus rhythm. Pirmenol concentrations were measured by high performance liquid chromatography.[8]

### STATISTICAL ANALYSIS

Analysis of variance was used to examine the significance of serial changes. We used Student's *t* tests for continuous variables and Fisher's exact test for discrete variables to compare differences between the treatment groups and between converters and non-converters. We used the Mann-Whitney rank sum test to examine differences in duration of fibrillation. Differences of $p<0{\cdot}05$ were regarded as statistically significant.

## Results

Age, left atrial and ventricular echocardiographic diameter, radiological heart volume, initial heart rate, duration of fibrillation, and use of digitalis and beta blockers were similar in the groups given active drug or placebo. Because there was a slight decrease in diastolic blood pressure ($p<0{\cdot}05$) and heart rate ($p<0{\cdot}0001$) in the 30 minute period of baseline observation, we used only the values obtained during the last 15 minutes as the basis for the comparison of responses.

### EFFECT ON RHYTHM

Sinus rhythm was restored in 12 (60%) of 20 patients on pirmenol and in three (15%) of 20 patients given placebo ($p<0{\cdot}01$). Conversion occurred 2–16 minutes after the first bolus of the active drug, but conversion times were randomly distributed in the placebo group (Figure). Sinus rhythm appeared after 50 mg of pirmenol in seven patients and after a total dose of 100 mg in five patients.

A nodal rhythm at a rate of 60 beats per minute appeared for 15 seconds after the first three sinus beats in one patient. Bradycardia or conduction disorders did not occur and there were no sinus arrests or escape rhythms in other patients. One patient who received a placebo injection developed non-sustained ventricular tachycardia, but none of the pirmenol group did so.

Fibrillation before treatment tended to last longer in non-converters than in converters ($0{\cdot}05<p<0{\cdot}1$; Table 1). More patients in the converter group than the non-converter group had used beta blockers (7/12 *vs* 1/8; $p=0{\cdot}07$). No significant differences were found in any of the other baseline characteristics (Table 1).

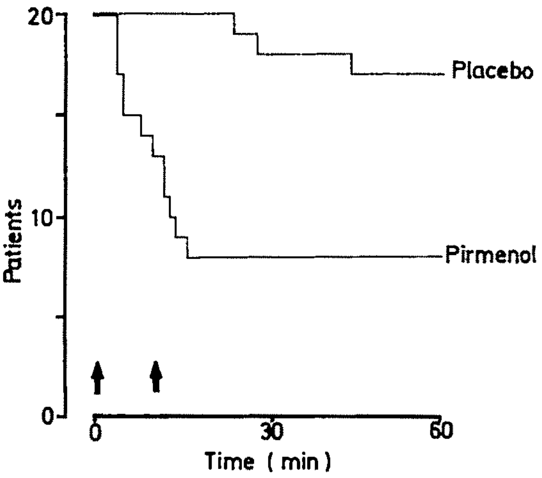

Figure *Conversion of atrial fibrillation to sinus rhythm in the pirmenol and placebo groups. Vertical line shows patients remaining in atrial fibrillation. The injection times are indicated*

Table 1 *Patient characteristics in the pirmenol group (mean (SD))*

| | *Converters (n = 12)* | *Non-converters (n = 8)* |
|---|---|---|
| Age (years) | 51 (19) | 49 (10) |
| Radiological heart volume (mm/m$^2$) | 410 (80) | 520 (180) |
| Initial heart rate (beats/minute) | 115 (19) | 99 (24) |
| Left ventricular end diastolic diameter (mm) | 51 (5) | 49 (8) |
| Left atrial diameter (mm) | 31 (6) | 34 (6) |
| Left ventricular fractional shortening | 0·32 (0·07) | 0·33 (0·08) |
| Duration of atrial fibrillation (h) | 8 (7) | 18 (14) |
| Serum potassium ion concentration on admission (mmol/l) | 3·8 (0·2) | 4·1 (0·2) |
| Heart disease* (n) | 6 | 4 |
| Previously documented atrial fibrillation (n) | 8 | 6 |
| History of high alcohol consumption (n) | 5 | 1 |
| Digitalis used (n) | 3 | 2 |
| Beta blockers used (n) | 7 | 1 |

*Coronary artery disease (4 patients), cardiomyopathy (2), hypertensive heart disease (3), atrial septal defect (1).

### RESPONSES IN HEART RATE AND BLOOD PRESSURE

Ventricular rate increased in eight non-converters by a mean of 19 beats/minute five minutes after the second bolus of pirmenol. The use of beta blocking agents influenced the changes in heart rate. The mean heart rate before conversion or after the second bolus in eight patients who took beta blockers did not increase, whereas in 12 patients who were not on beta blockers the mean increase was 17 beats/minute (Table 2). Use of digitalis did not influence the change in heart rate in patients on pirmenol.

There were no significant drug induced changes in systolic or diastolic blood pressure in the converter and non-converter groups nor in those patients who used a beta blocking agent. The lowest systolic blood pressure recorded in any patient was 104 mm Hg. There were no significant changes in the blood pressure or heart rate in the placebo group.

### ELECTROCARDIOGRAPHIC INTERVALS AND PLASMA CONCENTRATIONS OF PIRMENOL

There were mean increases in QRS duration and QT interval of 12 ms ($p<0\cdot01$) and 33 ms ($p<0\cdot001$) respectively 15 minutes after the first injection. The longest uncorrected and corrected (Bazett's formula) QT intervals in any patient were 440 ms and 490 ms respectively. No bundle branch block appeared. The mean (SD) plasma concentration of pirmenol five minutes after the first bolus was 1·3 (0·5) mg/litre. In patients who received a total dose of 100 mg, the concentration was 2·1 (0·8) mg/litre five minutes after the second bolus and 1·1 (0·3) mg/litre at the end of the 60 minute observation period.

No patient experienced any side effects and none had any chest pain or increased dyspnoea. Sinus rhythm was later achieved in all patients after a drug induced or electrical conversion.

## Discussion

This is the first report of the effects of pirmenol in paroxysmal atrial fibrillation. Other antiarrhythmic drugs have been given intravenously to convert non-established atrial fibrillation. Halpern *et al* showed that intravenous procainamide restored sinus rhythm in nine of 21 patients (43%)[9] and Fenster *et al* reported that procainamide restored sinus rhythm in 58% of patients with atrial fibrillation.[10] In a study by Camm *et al* disopyramide terminated atrial fibrillation in 10 of 14 subjects (71%).[11] A single bolus of intravenous amiodarone restored sinus rhythm in 46% of patients in 30 minutes.[12] Intravenous flecainide converted atrial fibrillation to sinus rhythm in 14 of 39 patients within 15 minutes.[13] Verapamil was successful in 8–15% of patients.[14-16]

Duration of fibrillation[10] and the size of the left atrium[9 17] influence the success of conversion. All the previously mentioned studies were largely performed in subjects with non-established paroxysmal or acute atrial fibrillation.[9-16] Although the duration of fibrillation varied between studies, making comparison of the therapeutic effects difficult, fibrillation had not lasted more than one day in most patients. The success rate (60%) of pirmenol resembles that of procainamide disopyramide, and amiodarone for short term intravenous use. All of these agents restore sinus rhythm rapidly.

Pirmenol increases the effective refractory period of the atria in man (unpublished). Increased refractoriness could result either from depression of the fast response channel or from prolongation of the action potential, both of which effects have been observed in rabbit atria.[5] A lengthening of the atrial effective refractory period theoretically reduces the number of disorganised activation wave fronts circulating in the fibrillating atria.[18] Defibrillation may be the result of the increased probability of a conduction block with extinction of re-entry due to prolonged refractoriness. Furthermore, experiments in rabbits indicate that synchronisation of atrial activation wave fronts or reduction in their number may enhance the effective conduction of the atrioventricular node and reduce the degree of concealed conduction in the atrioventricular node and hence increase the transmission of impulses to the ventricles.[19 20] The anticholinergic effect of pirmenol[21] probably also contributes to the increase in ventricular rate during atrial fibrillation.

A higher proportion of patients on beta blockers achieved sinus rhythm (7/8 *vs* 5/12; $p=0\cdot07$), and there was no increase in heart rate in those patients who were on beta blockers. Whether beta blocking agents were causally related to the success of conversion by pirmenol cannot be definitely established. It is unlikely that their use merely selected those

Table 2 *Heart rate responses (beats/minute) in patients in relation to conversion of atrial fibrillation and use of beta blockers. Values are mean (SD) at baseline and before termination of fibrillation or five minutes after the last bolus*

| | *No* | *Baseline* | *Pirmenol* | *p value for* | |
|---|---|---|---|---|---|
| | | | | *Change* | *Interaction between group and change* |
| Converters | 12 | 111 (20) | 116 (18) | NS | <0·05 |
| Non-converters | 8 | 94 (21) | 113 (19) | <0·01 | |
| Beta blocker | 8 | 102 (26) | 103 (18) | NS | <0·05 |
| No beta blocker | 12 | 106 (20) | 122 (14) | <0·01 | |

patients with a greater chance of conversion, because left atrial diameter or duration of fibrillation were no more favourable in those on beta blockers. Also, six of the eight patients had been on long term beta blockers treatment, and this indicates that these drugs were unable to prevent the paroxysm. Similar synergism between beta blockers and quinidine in atrial fibrillation has been suspected.[22]

The dosages of pirmenol tested and plasma concentrations obtained paralleled those which are effective in other arrhythmias. Similar doses (50 mg) given intravenously once or twice terminated paroxysmal supraventricular tachycardia,[4] and single short infusions of up to 150 mg abolished premature ventricular complexes.[2]

Rapid conversion of atrial fibrillation of recent onset by intravenous injection of a drug may avoid the need for electrical cardioversion and shorten hospital stay. A fall in blood pressure and depression of the sinus node and atrioventricular conduction system are potential adverse reactions of intravenous administration of drugs for conversion of atrial fibrillation.[9–11 14] Quinidine-like class I antiarrhythmics may also increase ventricular rate.[11] These untoward effects have prevented the use of intravenous conversion as a routine treatment. In the present study, from which patients with advanced cardiac diseases were excluded, restoration of sinus rhythm was uncomplicated except for a short period of nodal rhythm in one patient. Although the full electrophysiological effects of pirmenol are not known, by analogy with other fast inward current inhibitors[23–25] it is likely to depress impulse formation and conduction when it is used to treat arrhythmias associated with sinus and atrioventricular nodal disorders. None of our patients had a hypotensive reaction. Pirmenol is known to increase blood pressure slightly and has only a slight myocardial depressant effect.[26]

In conclusion, pirmenol has an antifibrillatory effect in the atria. Its efficacy seems comparable to that of the agents presently available for rapid conversion of atrial fibrillation. It is well tolerated by patients without congestive heart failure or a diseased sinus node.

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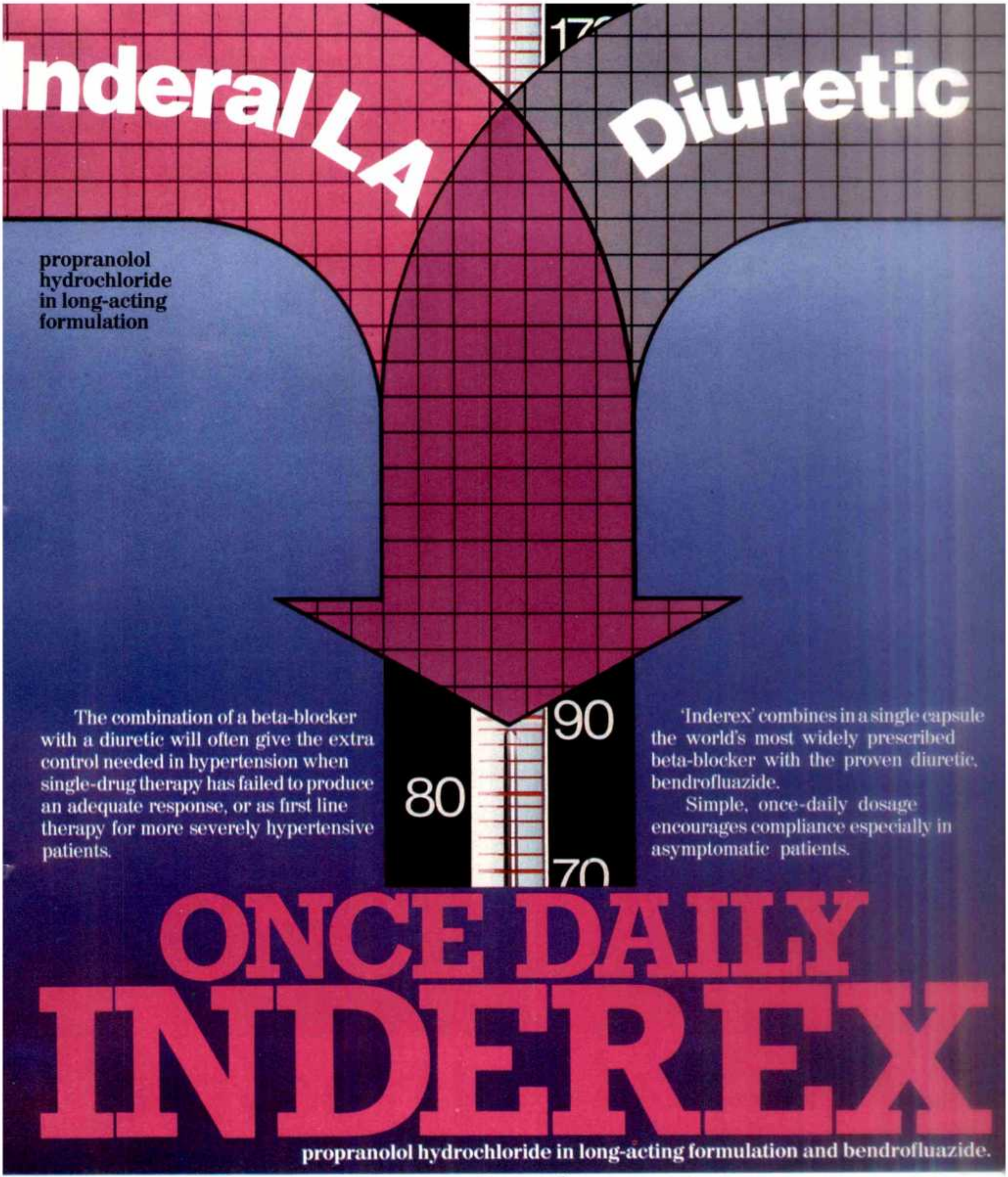

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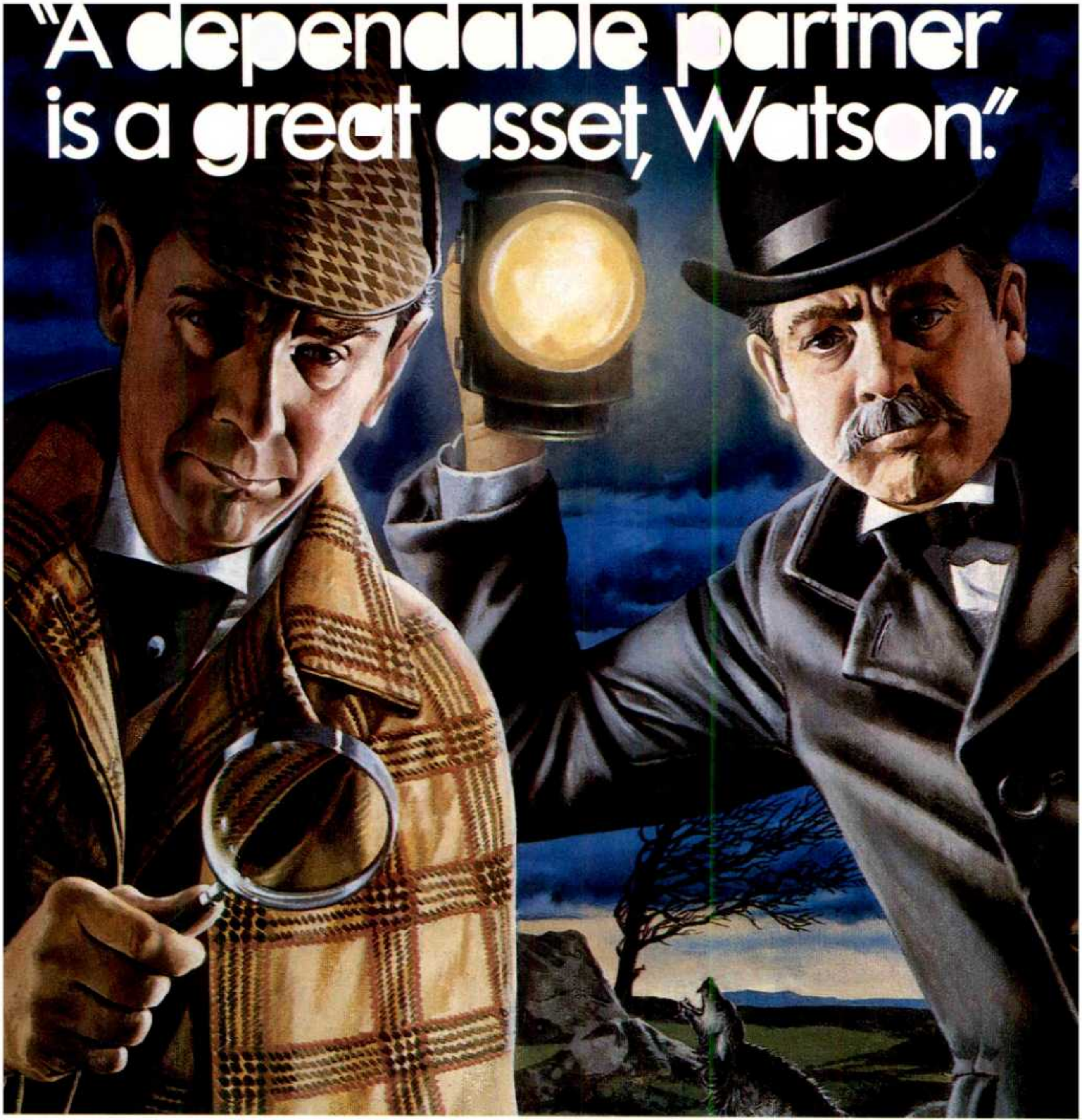
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**nces:** 1. Walker, R.G. et al, Med.J.Austral. (1981), **29,** (2), 235. 2. New Zealand Hypertension Study Group, NZ, Med.J. (1980), **92,** 341.

*Br Heart J* 1986; 55: 181–6

# Effect of long term treatment with metoprolol and sotalol on ventricular repolarisation measured by use of transoesophageal atrial pacing

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SUMMARY The effects of long term (4 weeks) treatment with oral metoprolol (100 mg twice daily) and sotalol (160 mg twice daily) on ventricular repolarisation time were compared in a double blind crossover study in 20 patients post-infarction. For QT interval studies transoesophageal atrial pacing was performed at a cycle length of 800 ms. Sotalol prolonged the QT interval by 5–7% compared with metoprolol. The prolongation reflects a change in the repolarisation time because there was no change in the QS interval. Measurements of heart rate at rest and during bicycle exercise indicated that metoprolol and sotalol in the doses selected were equipotent as beta blockers. Transoesophageal atrial pacing is a simple non-invasive method with few and mild side effects that is well suited to drug studies.

According to the Vaughan Williams classification, beta adrenergic receptor antagonists have class II antiarrhythmic properties that are characterised by a reduction of the spontaneous phase 4 depolarisation of pacemaker cells.[1] Some beta blockers, for example alprenolol and propranolol, also have a direct membrane stabilising (class I) effect that leads to a reduction in the maximum rate of rise of cardiac action potentials.[1] This antiarrhythmic effect has been seen when high concentrations of such drugs are used in vitro, but it is believed to be of no clinical importance.[2 3]

Metoprolol is a cardioselective beta blocker which has no intrinsic sympathomimetic activity and membrane stabilising properties.[4] Sotalol is a non-cardioselective beta blocker that has no important membrane stabilising or intrinsic stimulatory activity.[1 5] In contrast to other currently available beta blockers, sotalol has class III antiarrhythmic activity in that it increases the duration of the action potential after short term administration.[6 7] Some beta blockers including metoprolol have caused similar effects but only after long term treatment and to a lesser degree. Although recent studies in man have suggested that sotalol and other currently available beta blockers may have different effects on ventricular repolarisation after long term treatment as far as we know no double blind study has been performed to confirm this.[8 9] Craemer *et al* performed a randomised crossover study but this was not double blind.[10]

We have compared the effects of long term treatment with metoprolol (class II) and sotalol (classes II and III) on ventricular repolarisation in a double blind crossover study in patients who were already on chronic beta blocker treatment after a previous myocardial infarction. We used doses of metoprolol (100 mg twice daily) and sotalol (160 mg twice daily) with equipotent beta blocking effects.

## Patients and methods

We studied 20 men aged 46–64 years (mean 60 years) who had had a myocardial infarction more than one year before. They were on long term metoprolol treatment (minimum daily dose of 150 mg). None was on any other antiarrhythmic agent. We excluded patients with clinical signs of heart failure or severe angina (New York Heart Association functional class III–IV) and those with either partial or complete bundle branch block. To ensure measurable QT intervals we did not study patients with biphasic negative T waves or U waves in the surface lead V2. The

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Accepted for publication 27 September 1985

study protocol was approved by the ethical committee of the hospital, and each patient gave informed oral consent.

### METHODS

In this double blind crossover study the patients remained on their usual long term treatment with metoprolol during the run-in period. They were randomly allocated to receive oral sotalol 160 mg twice daily (10 patients) or metoprolol 100 mg twice daily (10 patients) for four weeks (period I). After this they were switched to treatment with the other tablet for another four weeks (period II). Investigations were performed during the run-in period and after both periods of treatment.

### ERGOMETER TEST

The patients underwent a bicycle ergometer test starting at a workload of 50 W which was increased by 10 W per minute. Heart rate, blood pressure, and a 12 lead electrocardiogram were monitored each minute. When the heart rate reached 70% of the predicted maximum pulse rate the exercise test was stopped. The effect of the beta blockade was evaluated and compared by measurement of heart rates at rest and during exercise.

### TRANSOESOPHAGEAL ATRIAL PACING

With the patient in a semirecumbent position, that is lying at approximately 40° to the horizontal, a bipolar electrode catheter was advanced into the distal oesophagus. We used flexible silicone rubber coated bipolar electrode catheters with an interelectrode distance of 18 or 28 mm (Medtronic 6992). The distal electrode was designated as the negative (cathode) electrode. Unipolar atrial electrograms were recorded from the catheter (Fig. 1a). The electrode position was adjusted to obtain a maximum positive unipolar atrial deflection from the distal electrode and a biphasic atrial electrogram from the proximal electrode. The minimum threshold current required to pace the atria reliably was determined by a technique described elsewhere.[11] A burning sensation causing slight epigastric discomfort was common during stimulation, but no sedative or other premedication was required. Transoesophageal bipolar atrial stimulation was undertaken for approximately three minutes at a basic cycle length of 800 ms (Fig. 1b). Atrial stimulation was performed with a programmable stimulator made in our own laboratory that delivers a constant current square-wave pulse. The pulse width was fixed at 10 ms. A precordial electrocardiogram was displayed on an oscilloscope and recorded on a Mingograph 82 (Siemens-Elema) as well as on a tape recorder (TEAC) during atrial stimulation.

### BLOOD SAMPLING

Blood samples were collected immediately after the investigations for later analyses of plasma concen-

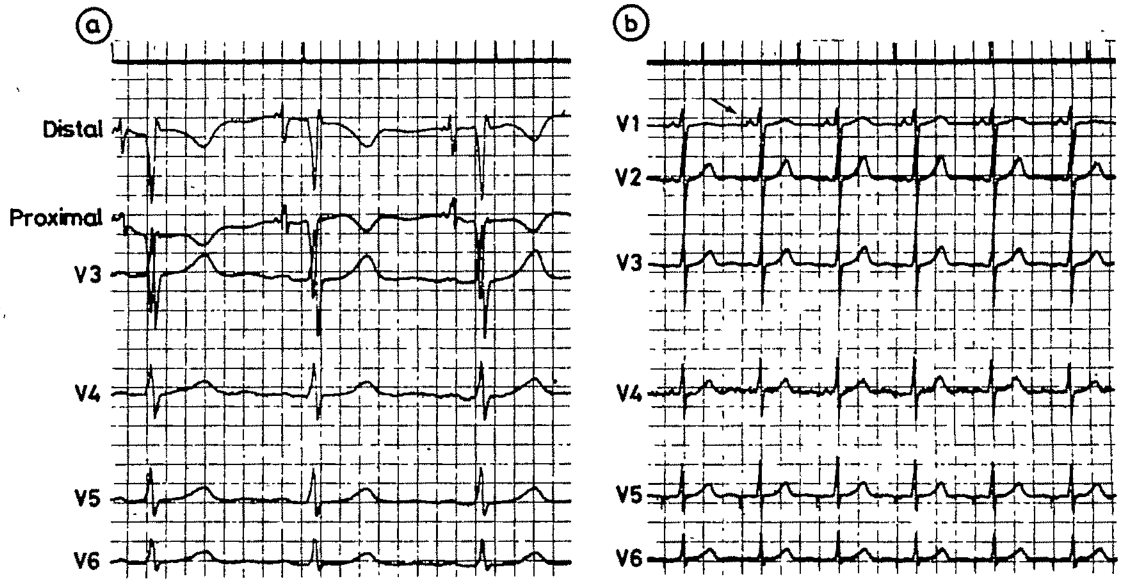

Fig. 1 *(a) A representative example of unipolar atrial electrograms recorded from the oesophageal electrode catheter. Paper speed 50 mm/s. (b) Recording of transoesophageal bipolar atrial pacing from the same patient as in (a). Atrial stimulation was performed at a basic cycle length of 800 ms. The arrow indicates the stimulus spike. Paper speed 25 mm/s.*

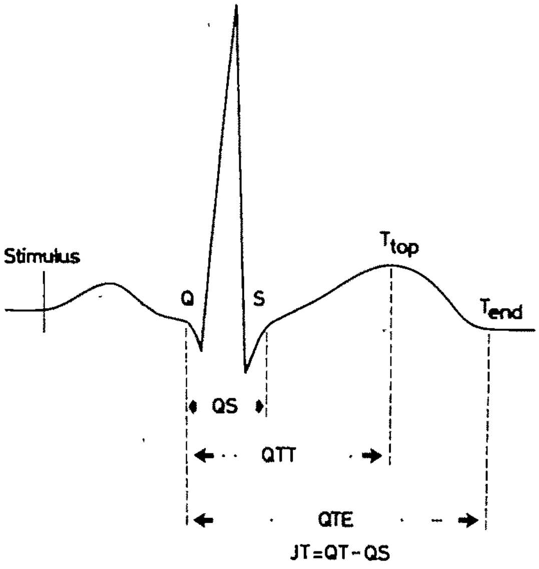

Fig. 2 *The following intervals were analysed: QS (from the beginning of the Q wave to the end of the S wave), QTT (from the beginning of the Q wave to the top of the T wave), and QTE (from the beginning of the Q wave to the end of the T wave). The JT interval was calculated by subtracting the QS interval from the QT interval. All intervals were measured at a paper speed of 100 mm/s.*

trations of metoprolol and sotalol.

### COMPUTERISED ANALYSIS OF THE QRST INTERVALS

We used a specially developed interactive computer program to analyse the following variables: QS, QT top, QT end, JT top, and JT end (as defined in Fig. 2). All measurements were made from lead V2 (except for one patient where V3 was used because of lack of signal). The intervals were all measured at a fixed basic atrial pacing cycle length of 800 ms. A representative sample of each recording saved on tape was displayed on the oscilloscope. For the first beat chosen, the operator defined the following seven points: start of the pacemaker stimulus, start of the Q wave, top of the R wave, negative top of the S wave, end of the S wave, top of the T wave, and end of the T wave. For the subsequent analysed beats these points were outlined by the program but could be corrected if necessary. Only signals that were preceded by constant and adequate pacing were analysed. All the results are the means of at least five representative complexes. The output consisted of a table of each individual variable for all accepted beats as well as the mean values and standard deviations.

### QTc CALCULATION

QTc is usually calculated by the Bazett formula from the QT interval measured during sinus rhythm. In the present study the QTc was calculated from the QT intervals measured during transoesophageal atrial pacing at a basic cycle length of 800 ms.

### STATISTICAL METHODS

We used the two-tailed Student's *t* test to compare paired differences. The level of statistical significance was set at a $p < 0{\cdot}05$, but all p values are given.

## Results

Fifteen out of 20 patients were included in the QT interval analysis. The reasons for exclusion were as follows: one patient was excluded during run-in because he developed hypotension, sweating, and dizziness and slight bradycardia when transoesophageal atrial pacing was started. The symptoms and physical findings were observed shortly after pacing was started, and stimulation was discontinued before reliable atrial pacing could be obtained. The patient reported no pain. Blood pressure returned to normal after the patient was tilted in the head down position. In another patient an intolerable headache developed during blind period 1 (sotalol) and the medication was discontinued after 11 days. Three patients had biphasic negative T waves or prominent U waves in one or more recordings that made subsequent comparisons of QT intervals impossible. They completed the study but were excluded from QT interval analyses.

Thus atrial pacing was performed without side effects in 18 of 19 patients on three consecutive occasions. The means of the thresholds for adequate pacing were: 19 mA (run-in), 21 mA (metoprolol), and 22 mA (sotalol) (range 7–36 mA).

### HEART RATE

The heart rates at rest and during exercise (measured at a workload of 100 W) were not significantly different on the two treatments (Table). This indicates that a similar degree of beta blockade was induced by the two agents.

### QS INTERVALS

There was no significant change in the QS interval, which was within the normal range (Table) on both agents.

### QTT AND QTE INTERVALS

Treatment with sotalol was associated with a significantly longer QTT interval than treatment with metoprolol (mean (SD)) (319 (18) ms *vs* 301

Table *Comparisons of heart rate and QRST intervals (ms) during run-in and after 4 weeks' treatment with metoprolol or sotalol*

| *Results* | *Run-in* | *M* | *S* | *M vs run-in (p)* | *S vs run-in (p)* | *S vs run-in (% change)* | *S vs M (p)* | *S vs M (% change)* |
|---|---|---|---|---|---|---|---|---|
| Heart rate at rest (bpm) | 58 (16) | 55 (8) | 57 (10) | NS | NS | — | NS | — |
| Heart rate at 100 W (bpm) | 96 (20) | 92 (11) | 95 (14) | NS | NS | — | NS | — |
| QS | 98 (12) | 99 (11) | 100 (9) | NS | NS | — | NS | — |
| QT top | 300 (11) | 301 (16) | 319 (18) | NS | <0·001 | + 6 | <0·001 | + 6 |
| QT end | 421 (17) | 414 (25) | 436 (25) | NS | <0·001 | + 4 | <0·001 | + 5 |
| JT top | 202 (16) | 202 (19) | 219 (23) | NS | <0·001 | + 8 | <0·001 | + 8 |
| JT end | 324 (24) | 316 (26) | 336 (28) | NS | <0·005 | + 4 | <0·001 | + 6 |
| QTc top | 330 (10) | 340 (20) | 360 (20) | NS | <0·001 | + 9 | <0·001 | + 6 |
| QTc end | 470 (20) | 460 (30) | 490 (30) | NS | <0·005 | + 4 | <0·001 | + 7 |

Run-in, long term treatment with metoprolol at a minimum daily dose of 150 mg; M, after four weeks' treatment with metoprolol (100 mg × 2); S, after four weeks' treatment with sotalol (160 mg × 2).

(16) ms, +6%; $p<0{\cdot}001$). Sotalol also prolonged the QTE interval (436 (25) ms *vs* 414 (25) ms, +5%, $p<0{\cdot}001$) (Table and Fig. 3).

### QTc

We used Bazett's formula to calculate the QTc from the QT intervals measured during atrial pacing. The QTc top was 340 (20) ms during metoprolol and 360 (20) ms during sotalol treatment ($p<0{\cdot}001$). The QTc end was 460 (30) ms (metoprolol) and 490 (30) ms (sotalol) ($p<0{\cdot}001$) (Table).

### JTT AND JTE INTERVALS

The JTT and JTE intervals increased by 8% and 6% respectively ($p<0{\cdot}001$) during treatment with sotalol compared with metoprolol (Table).

### PLASMA CONCENTRATIONS

The plasma concentration of metoprolol in 15 samples about five hours after one oral dose was 41–700 nmol/l (mean 265 nmol/l). The plasma concentration of sotalol in 14 samples was 0·8–2·0 µg/ml (mean 1·4 µg/ml). One sample was lost.

## Discussion

The antiarrhythmic efficacy of beta blockers may be the result of their ability to oppose the effects of

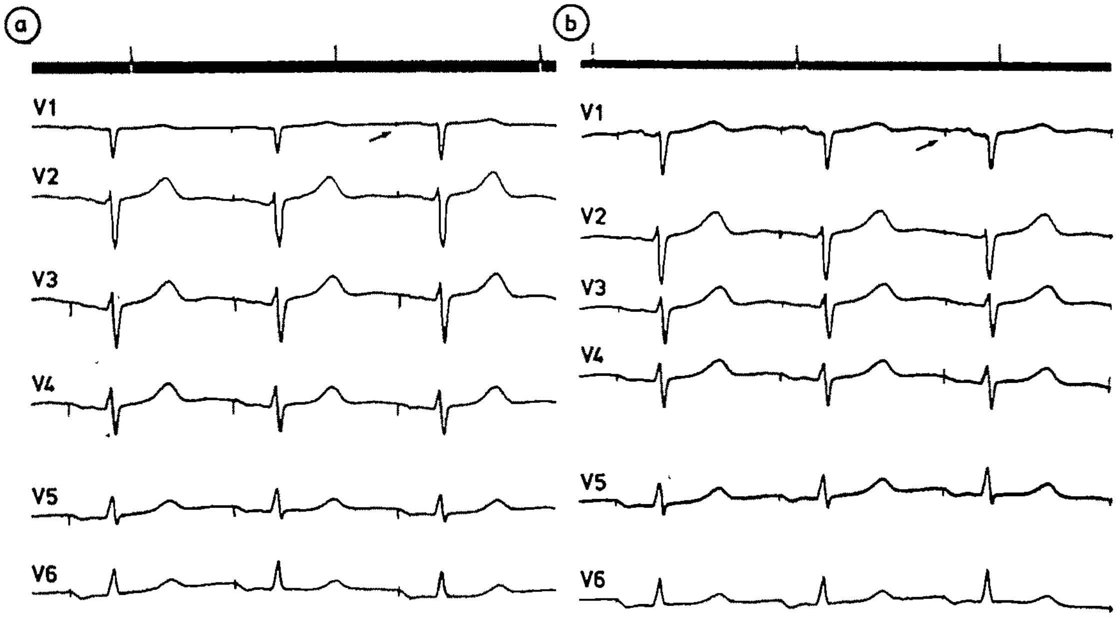

Fig. 3 *Electrocardiograms obtained during atrial pacing from one patient. They show the QT intervals during treatment with metoprolol (a) and sotalol (b). The arrow indicates the stimulus spike. Paper speed was 50 mm/s.*

catecholamines on automaticity and conductivity. Animal studies have shown that several beta blocking agents with different pharmacological properties produce a moderate prolongation of the ventricular repolarisation time when they have been given for four weeks.[12 13] This contrasts with that lack of effect after short term administration. In healthy volunteers metoprolol prolonged the right ventricular repolarisation time by 6–8% after five weeks' treatment with 400 mg daily; short term administration of metoprolol had no effect.[9]

In contrast, short term administration of sotalol, which was initially described as a pure beta adrenergic antagonist with class II activity, considerably increased the action potential duration.[6 7] This class III mode of action was recently confirmed in patients with atrial fibrillation. Sotalol prolonged the right ventricular repolarisation time by about 13–17% after intravenous administration of 100 mg, and this effect was maintained after twelve weeks of oral treatment.[8] This is consistent with other reports demonstrating a prolongation of QT and JT intervals after short term administration of sotalol.[14] The mechanism by which beta adrenergic blockers such as metoprolol prolong the ventricular repolarisation time after chronic treatment is not yet known. It has been proposed that this effect represents a myocardial adaptation to prolonged beta blockade.[15]

In order to clarify whether long term treatment with a beta blocker without class III activity would prolong the ventricular repolarisation time to the same extent as an antiarrhythmic agent with combined class II and III activity, it seemed logical to use sotalol as a standard for comparison. The ventricular repolarisation time may be assessed from the QT intervals, ventricular effective refractory periods, and ventricular monophasic action potentials. Recent studies with beta adrenergic blockers have shown consistent changes in these indices after long term treatment.[9]

Difficulties with defining the end of the T wave make measurement of the QT interval uncertain.[16] To ensure more easily defined intervals we also included the QT top interval. The QT interval is frequency dependent and the most widely applied rate correction factor has been Bazett's formula. The formula was intended to correct the values to a heart rate of 60 beats per minute, but will give an overcorrection of the QT interval at high rates and an undercorrection at low heart rates. When Bazett's formula is used for correction during sinus rhythm, slight or even moderate drug induced changes might therefore be masked, as they were in other drug studies.[17] If, however, the heart rate is kept constant, the measurements will contain a systematic error but will allow drug induced changes to be detected. To circumvent the use of a correction factor some previous studies have compared QT intervals at identical and constant paced heart rates by means of intracardiac atrial stimulation.[10 17]

To ensure the detection of even minor drug induced changes and to avoid an invasive intervention, we have compared QT intervals at a fixed paced heart rate produced by transoesophageal atrial stimulation. We performed transoesophageal atrial pacing on 56 different occasions and on only one (1·8%) occasion was there a complication, judged to be a vasovagal reaction.

The electrode catheter insertion depth is carefully controlled to minimise the pacing threshold and the appropriate depth may be predicted by the site of the maximum atrial electrogram or the patient's height.[11] In the present study, the threshold for adequate atrial pacing was found in most patients when the atrial electrogram from the proximal electrode showed a biphasic deflection and the distal electrode a highly positive atrial deflection, and this accords with other studies.[11] The mean minimum pacing threshold was of about the same magnitude for all three pacing sequences in the same patient when pacing was performed from identical positions.

The minimum current required for atrial pacing varies among different investigators. In one study, atrial capture was achieved in 75% of the attempts when a current of 17·5 mA was used.[18] Others have reported an average minimum pacing threshold of 10 mA (range 4·5–20 mA).[11] The minimal thresholds obtained in the present study were somewhat higher than those reported by other investigators, but no patient complained of intense discomfort. The currents used in this study were considerably below those reported to produce hyperaemia or epithelial erosion in canine experiments.[19 20] Epithelial erosion appeared after pacing at 60 mA at a pulse width of 2 ms for 4 hours, but no injury was noted when the pacing time was limited to < 30 minutes.

We found that four weeks' treatment with sotalol significantly prolonged the QT intervals by 5–7% more than metoprolol (Table). The prolongation was confined to the JT interval, as there was no significant difference in the QS interval, and this must therefore reflect a change in the ventricular repolarisation time. This is consistent with results from other studies, although the groups of patients studied were not comparable.[8 9 21] The QT top and the QT end intervals showed consistent changes, which suggests that the former may be used with advantage, especially when the end of the T wave is obscured. The QTc showed similar and statistically significant changes when calculated from a fixed paced heart rate. The QTc was not calculated during sinus rhythm. The heart rates at rest and the heart rates during exercise were not significantly different on the two treatments, hence the difference in the repolarisation time cannot be attributed to unequal beta blockade.

Even though long term administration of various beta blockers may result in a class III like mode of action, this study and those of others indicate a quantitative difference between these agents and sotalol. Unlike metoprolol, sotalol significantly and selectively prolonged ventricular refractoriness in infarcted zones compared with normal myocardium after short term administration in dogs.[22] In the same study sotalol significantly prevented and slowed ventricular arrhythmias in ischaemic myocardium; metoprolol did not have this effect. Whether this effect is due to the class III property of sotalol or to other differences (beta$_2$ blockade) is not known.

In conclusion, sotalol significantly prolonged the QT interval by 5–7% compared with metoprolol after four weeks' treatment. The prolongation reflects a change in the repolarisation time, since no significant change in the QS interval was noted. As the QT top and QT end intervals showed consistent changes, the former may be used when there are difficulties in defining the end of the T wave. No rate correction factor was required to obtain these QT interval changes because they were measured at a fixed heart rate. Transoesophageal atrial pacing was found to be a simple non-invasive method with few and relatively mild side effects. The method is well suited for drug studies requiring measurements at fixed heart rates.

This study was supported by grants from the Medical Society of Gothenburg and the Swedish National Association Against Heart and Chest Diseases.

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*Br Heart J* 1986; 55: 187–90

# Intravenous captopril treatment in patients with severe cardiac failure

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SUMMARY The effect of intravenous captopril was studied in 26 patients with severe chronic heart failure. Fourteen patients received a 25 mg intravenous bolus dose and 12 patients were given a series of incremental intravenous doses over the range 0·3125–45 mg. After the 25 mg bolus dose there was a rapid reduction in systemic vascular resistance and systemic blood pressure. The effect was greatest five minutes after the dose when cardiac output was increased by 20%. Mean right atrial pressure and pulmonary end diastolic pressure fell more slowly and reached their nadir 60 minutes after administration. Plasma free captopril concentration was significantly correlated with percentage reduction in systemic vascular resistance 15 minutes after the bolus injection, but was not correlated with either changes in right atrial or pulmonary artery pressures. With the series of incremental doses there was a progressive fall in systemic vascular resistance until a cumulative dose of 5·0 mg was reached; beyond this there was no further significant change.

The rapid response to intravenous captopril indicates that it may be useful in the treatment of patients with severe heart failure who require intensive treatment. After intravenous injection of captopril haemodynamic responses in patients with heart failure were greatest at plasma concentrations of 100 g/ml to 150 ng/ml. This is considerably higher than the plasma free captopril concentrations found after conventional oral doses of captopril.

Captopril, an angiotensin converting enzyme inhibitor, has become established as a treatment for severe chronic cardiac failure.[1-5] Until now only oral formulations have been available for clinical studies. To assess the feasibility of intravenous captopril treatment in patients with severe heart failure we have studied the haemodynamic responses to the administration of (*a*) a 25 mg bolus dose of intravenous captopril and (*b*) a series of incremental intravenous doses. The haemodynamic responses were compared with the time-profile of changes in plasma free captopril concentration and plasma renin activity.

## Patients and methods

### PATIENTS

We studied 26 patients (17 men and 9 women, mean age (SE) 60 (2) years, range 36–76). Fourteen received a bolus dose and 12 were given incremental doses. All patients had breathlessness at rest or on mild exertion (New York Heart Association functional class III or IV) despite regular treatment with digoxin and diuretic (frusemide ≥120 mg/day or bumetanide ≥4 mg/day). Each patient had severe myocardial impairment; this was secondary to ischaemic heart disease in 17 patients, to cardiomyopathy in six, and to rheumatic heart disease in three patients. The isotopically determined left ventricular ejection fraction (mean (SE)) was 19 (2)% (range 6–38%). Patients had fasted overnight and had not taken other medications on the day of study. Vasodilator treatment had been stopped at least three days before.

### HAEMODYNAMIC RECORDINGS

The patient remained supine throughout the study period. Right atrial and pulmonary arterial pressures and cardiac output were measured with a triple

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Accepted for publication 8 October 1985

lumen flow directed thermodilution catheter. Zero for pressure recordings was taken at 10 cm above table height. Cardiac outputs were measured in triplicate. Systemic arterial pressure was recorded at the arm by an electronic sphygmomanometer (Copal digital sphygmomanometer: UA251).

### PLASMA FREE CAPTOPRIL CONCENTRATION

N-ethylmaleimide (10 mg) was added to 5 ml plasma which had been separated in a refrigerated centrifuge immediately after withdrawal of the blood sample. Plasma free captopril concentration was measured by radioimmunoassay.[6] The coefficient of variation of the assay is 7·5% with a minimum detection limit of 2 ng/ml in plasma.

### PLASMA RENIN ACTIVITY

Plasma renin activity was measured by the method of Drury and Edwards.[7] The normal range for supine subjects is 0·3–1·5 ng/ml/h.

### BOLUS INTRAVENOUS CAPTOPRIL DOSE

A 25 mg bolus dose of captopril was given to 14 patients. Each had tolerated a 6·25 mg oral test dose three days earlier. After the insertion of the thermodilution catheter and after haemodynamic measurements had stabilised, three control recordings were made at 15 minute intervals. The 25 mg dose of intravenous captopril was then injected at a constant rate over 5 minutes. Haemodynamic recordings and blood samples for plasma free captopril concentration and plasma renin activity were taken at 5, 15, 30, 45, 60, 75, and 90 minutes after the end of injection. An additional measurement of systemic arterial pressure was taken at 2·5 minutes.

### INCREMENTAL INTRAVENOUS CAPTOPRIL DOSES

After control recordings, 12 patients received bolus doses of 0·3125, 0·3125, 0·625, 1·25, 2·5, 5·0, and 10·0 mg of captopril at 15 minute intervals, corresponding to cumulative dosages of 0·3125, 0·625, 1·25, 2·5, 5·0, 10·0, and 20·0 mg of captopril. Four patients received an additional final 25 mg dose of captopril. Each dose was injected over 30 seconds. Haemodynamic recordings and blood samples were taken immediately before each incremental dose of captopril.

### STATISTICAL ANALYSIS

The following statistical tests were performed on a PDP11/44 computer with Minitab statistical package: Student *t* tests, analysis of variance, and correlation coefficients. All figures are mean (SE).

## Results

Figure 1 shows the haemodynamic changes found after the 25 mg intravenous bolus dose. Systemic vascular resistance, mean systemic arterial pressure, and cardiac output changed rapidly, with maximal changes occurring at five minutes after the dose. Pulmonary end diastolic pressure and mean right atrial pressure fell more slowly reaching a nadir at 60 minutes after captopril. The Table shows the means of individual maximum changes. Plasma free captopril concentration was 2106 (417) ng/ml at 5 minutes after end of injection and fell to 75 (12) ng/ml at 90 minutes. The plasma free captopril concentration and percentage reduction in systemic vascular resistance were significantly correlated at +15 minutes ($r=0·60$, $p=0·02$). The plasma free captopril concentration and percentage reduction in mean right atrial pressure were not significantly correlated.

Figure 2 shows the haemodynamic response and plasma free captopril concentration after each incremental dose. There was a progressive change in systemic vascular resistance up to a cumulative dose

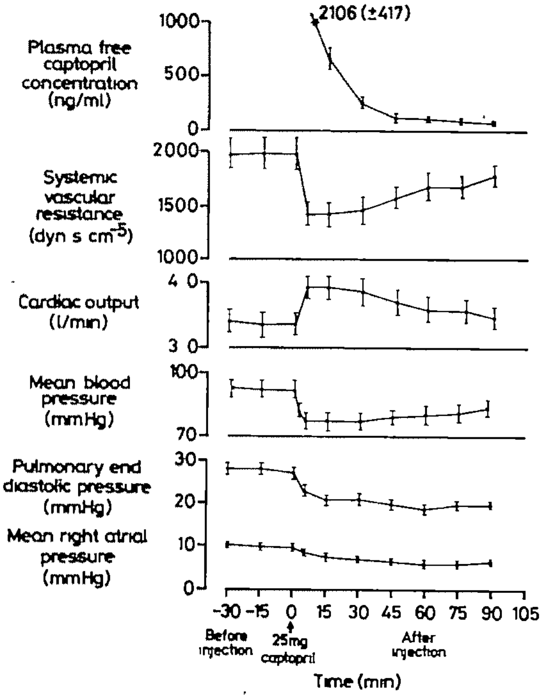

Fig. 1 *Time profile of mean (SE) haemodynamic response after a 25 mg intravenous bolus dose of captopril was injected over 5 minutes in 14 patients with severe chronic heart failure. (Time 0, end of injection.)*

Table *Maximal haemodynamic changes after a 25 mg intravenous bolus dose of captopril in 14 patients (mean (SE))*

| | *Basal* | *Maximal change* | *% change* | *p value** |
|---|---|---|---|---|
| Systemic vascular resistance (dyn s cm$^{-5}$) | 1994 (138) | 1380 (100) | −31% | <0·001 |
| Mean systemic pressure (mm Hg) | 93 (4) | 76 (4) | −18% | <0·001 |
| Cardiac output (l/min) | 3·43 (0·18) | 4·11 (0·22) | +20% | <0·001 |
| Pulmonary artery end diastolic pressure (mm Hg) | 25 (2) | 18 (2) | −28% | <0·001 |
| Mean right atrial pressure (mm Hg) | 10·2 (1·1) | 5·9 (1·1) | −42% | <0·001 |
| Heart rate (beats/min) | 86 (5) | 77 (5) | −10% | <0·001 |

*Analysis of variance.

of 5 mg; beyond this no further significant change was recorded (analysis of variance). The four patients given an additional final dose of 25 mg captopril (total cumulative dose 45 mg) did not have any further change with this additional dose (data not shown).

Six patients given a 25 mg intravenous bolus dose had plasma free captopril concentration and plasma renin activity measured for up to 24 hours after the dose (Fig. 3). The half life for plasma free captopril measured between 1·5 and 8 hours was 3·36 (0·25) h. Volume of distribution was 3·96 (0·53) l/kg and the clearance was 0·81 (0·07) l/kg/h. In these six patients plasma renin activity rose from a mean control value of 9·1 (3·7) ng/ml/h to a maximum of 65·6 (25·4) ng/ml/h 45 minutes after the injection of a 25 mg bolus ($p<0·05$).

## Discussion

An intravenous bolus of 25 mg captopril produced a very rapid reduction in systemic vascular resistance and caused almost immediate changes in cardiac output and systemic blood pressure. This is in keeping with the fact that angiotensin converting enzyme is located principally in the body's central compartment, that is the blood and lungs. The reduction in mean right atrial pressure and pulmonary end diastolic pressure was biphasic with a rapid initial fall followed by a continued decline to the nadir at 60 minutes after injection. This finding supports the concept that the effect of captopril on venodilatation may not be identical to the effect on systemic resistance.[8-12] The rapid response to intravenous doses indicates that intravenous captopril may have

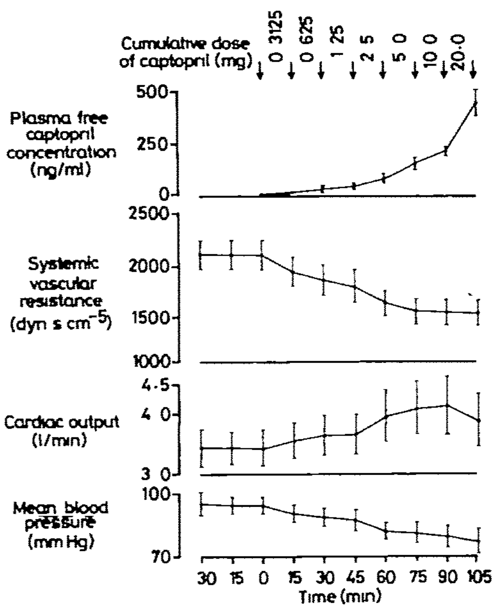

Fig. 2 *Profile of mean (SE) haemodynamic response after incremental doses of intravenous captopril in 12 patients with severe chronic heart failure.*

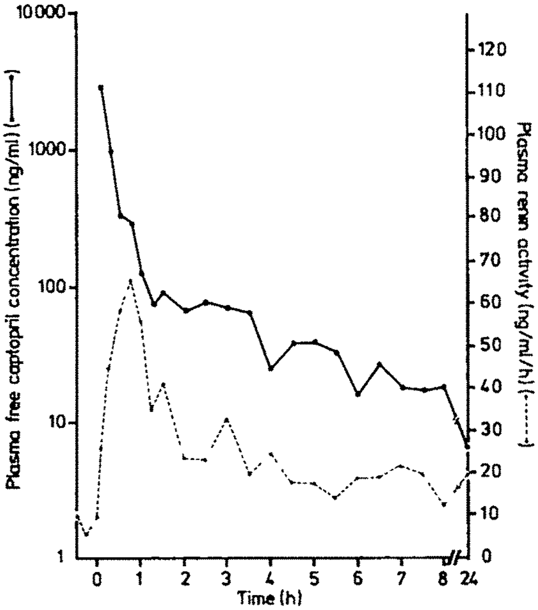

Fig 3 *Plasma free captopril concentration and plasma renin activity after a 25 mg intravenous dose of captopril in six patients with severe chronic heart failure.*

a place in the treatment of patients with heart failure who require intensive treatment.

The results of the incremental dosage study indicate that in patients with heart failure there is a progressive increase in response between 0·3125 mg and 5·0 mg of intravenous captopril and that a dosage range of 0·5–5·0 mg could be used to titrate the response in patients on intravenous treatment. Preliminary work in patients with hypertension suggest that they have a different dose response relation.

The effects of the 25 mg bolus of captopril on systemic vascular resistance, cardiac output, and systemic pressure were not sustained at the maximum level and the reduction in systemic vascular resistance fell from 28% to 9% by 90 minutes after the dose. Mean plasma free captopril concentration had fallen to 75 ng/ml by then. In the patients receiving incremental doses the plateau of response was reached at a mean plasma free captopril concentration of 128 ng/ml. This suggests that a maximal haemodynamic response to captopril in patients with heart failure may require plasma free captopril concentrations in the range of 100–150 ng/ml. This is considerably higher than the plasma free captopril concentration found before dosage in cardiac patients maintained on 12·5–25 mg of captopril given orally three times a day.[13] Though it is difficult to correlate the short term haemodynamic response and long term response to captopril, these data suggest that a higher dose or more frequent administration of captopril may be needed to maintain a maximal haemodynamic response.

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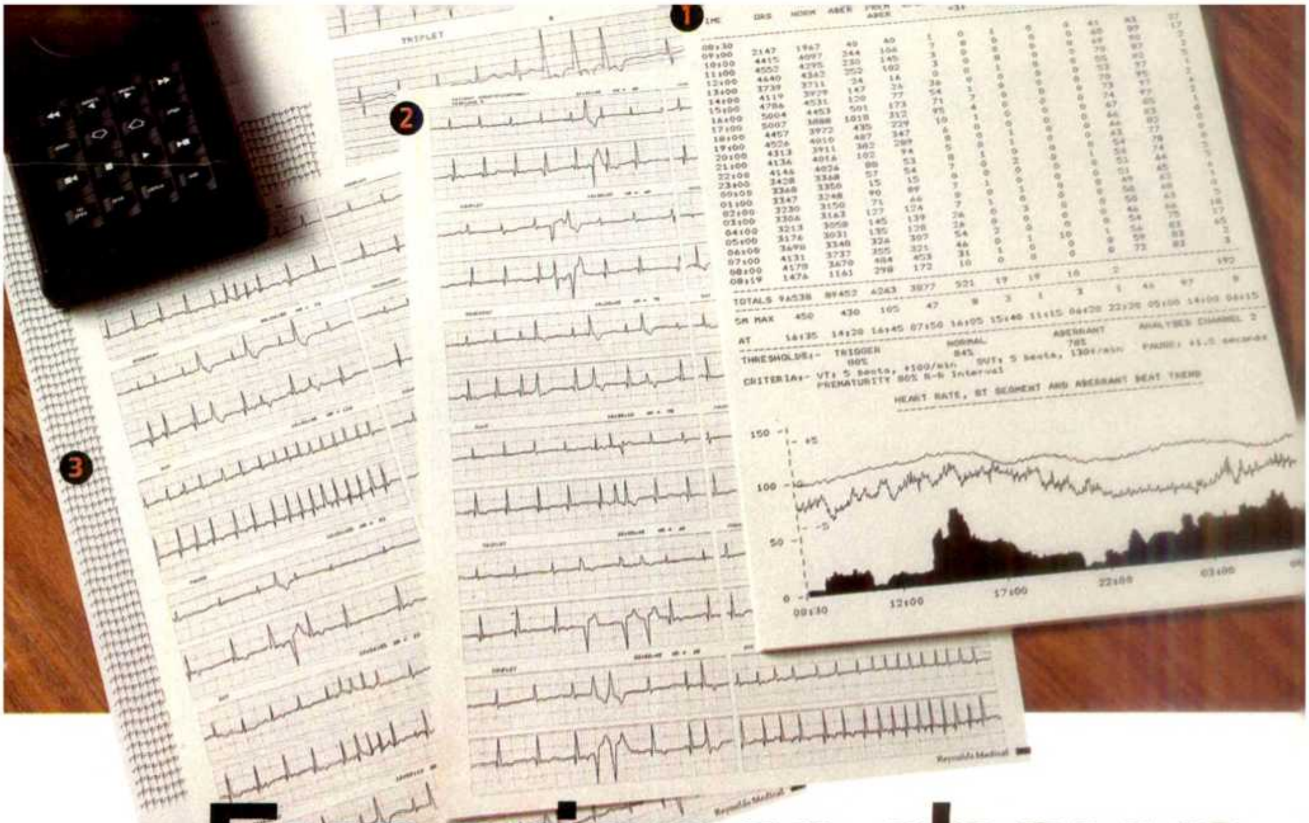

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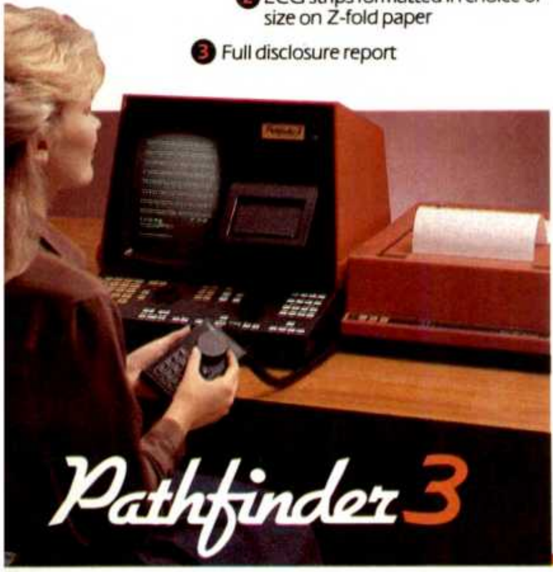

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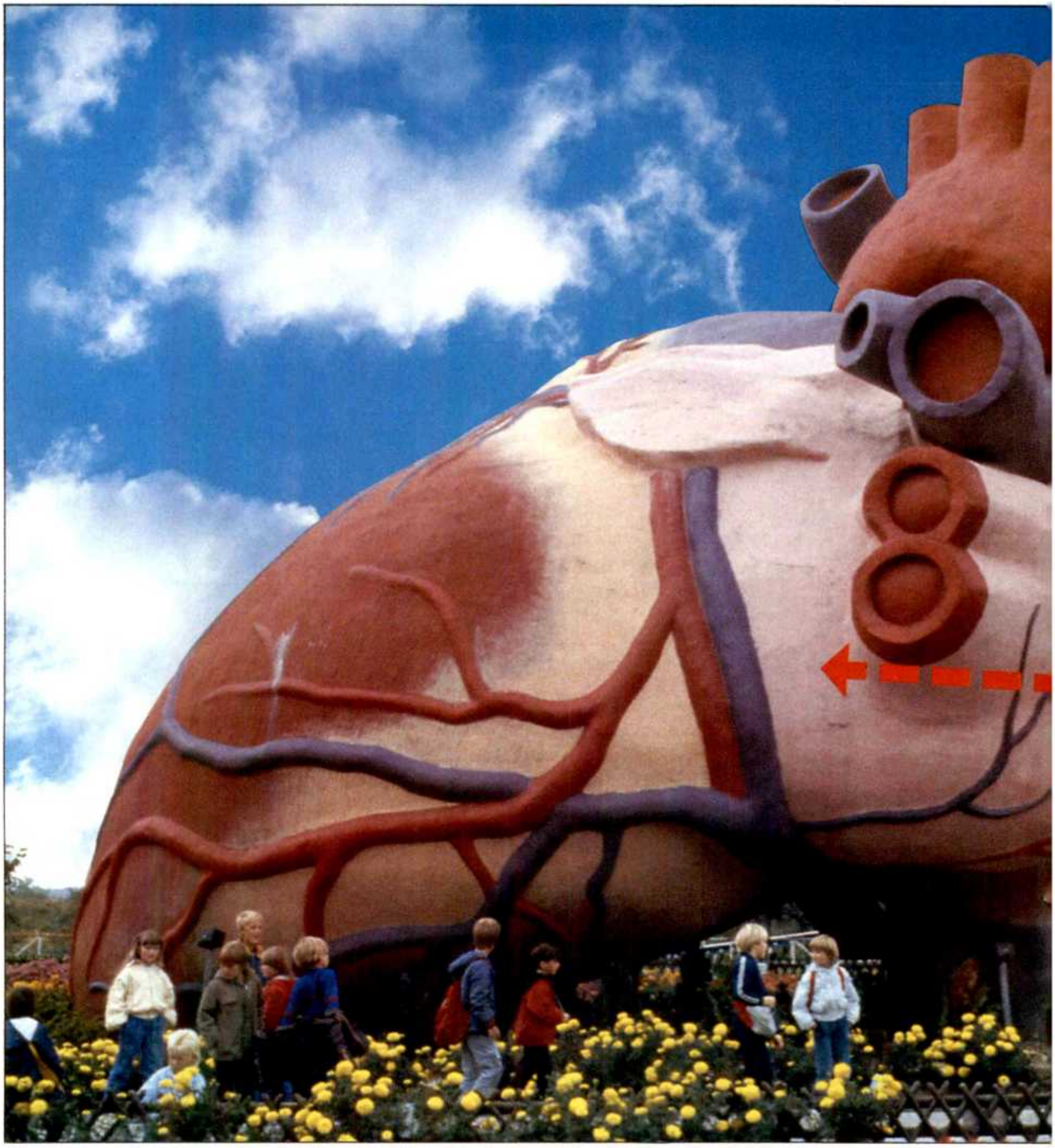

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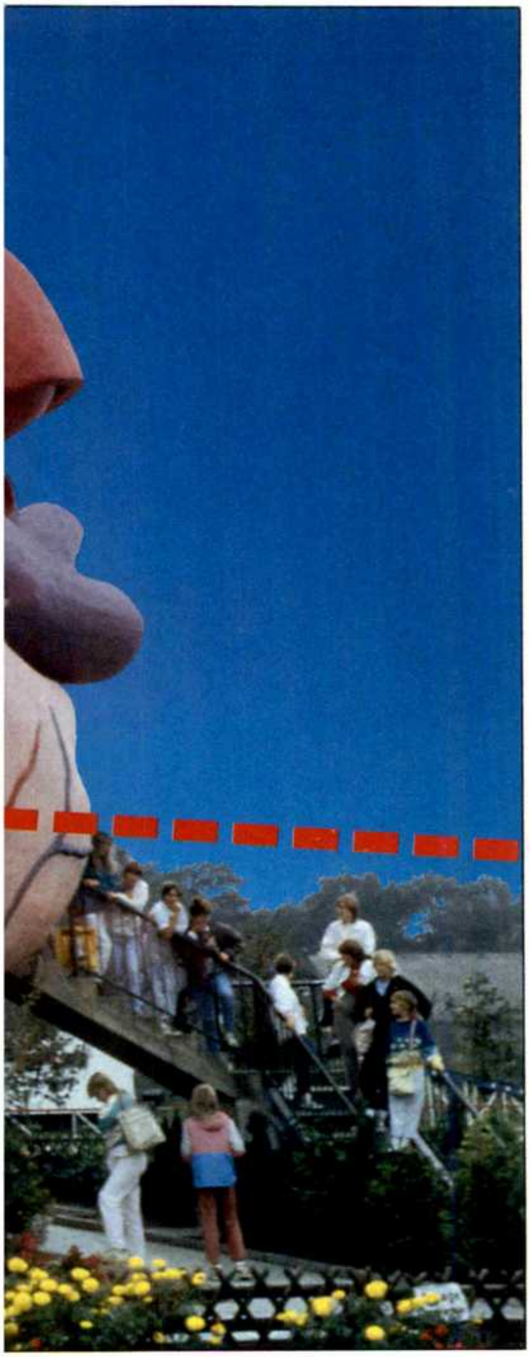

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*Br Heart J* 1986; 55: 191–7

# Heart failure associated with infective endocarditis

## *A review of 40 cases*

M P S VARMA,* D R McCLUSKEY,† M M KHAN, J CLELAND, H O O'KANE, A A J ADGEY

*From the Regional Medical Cardiology and Surgical Cardiology Centres, Royal Victoria Hospital, Belfast*

SUMMARY Thirty one (78%) of 40 consecutive patients (aged 13–79, mean 44 years) with infective endocarditis had congestive heart failure at presentation. Twenty six (65%) had had rheumatic heart disease and 17 (43%) patients had prosthetic valves. Eight (20%) patients had undergone dental procedures within three months of presentation. Blood cultures were positive in only 22 (55%) of the patients. In nine (41%) of them streptococci of the viridans group were isolated and in seven (32%) patients endocarditis was due to *Staphylococcus aureus*. Eight patients had Q fever endocarditis. Sixteen patients required operation because of haemodynamic deterioration while they were in hospital; 11 patients had native valves and five had prosthetic valves. Seven had emergency operations and were pyrexial at that time. Four of the seven died in hospital. Of the 12 who were alive and well after surgery only two required further surgery two and three years after the initial operation.

Twelve (30%) of the 40 patients died in hospital; in 10 death was mainly due to left ventricular failure or congestive heart failure. All patients died who had renal failure (four cases), myocardial infarction (two cases), complete heart block (one case), or ventricular fibrillation (two cases) before operation. Six (33%) of the 18 patients with culture negative endocarditis died. Two of the four patients seen and treated more than 12 weeks after the onset of symptoms died, as did three of the five patients with prosthetic valves who required surgery while in hospital. Three patients with neurological complications survived and only two (29%) of the seven patients with blood cultures that were positive for *Staphylococcus aureus* died.

Of these 40 high risk patients optimal antibiotic treatment and early surgery for haemodynamic difficulty ensured that 28 (70%) were discharged from hospital alive and well.

There are no accurate figures for the incidence of infective endocarditis in the United Kingdom, but it has been estimated that there are currently 40–50 cases per 1·8–2 million population per year.[1] The incidence of the disease does not seem to have fallen with antibiotic use. Infective endocarditis remains an important cause of mortality and morbidity, with rheumatic heart disease as its chief underlying cause, though to a much lesser extent today than a few decades ago. Heart failure significantly increases the risk of death in patients with infective endocarditis managed either medically or medically and surgically.

We have reviewed the presentation, management, and short term outcome in 40 consecutive patients with infective endocarditis. Thirty one (78%) of them presented clinically in congestive heart failure and in nine there was difficulty in establishing the diagnosis of infective endocarditis mainly because of negative blood cultures. All patients were admitted to this hospital between 1974 and 1980 during the acute phase of the illness.

## Patients and methods

The patient was considered to have endocarditis if the clinical picture was suggestive of the disease and blood cultures or serology were positive, or if in the presence of negative blood cultures the clinical pic-

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Accepted for publication 5 November 1985

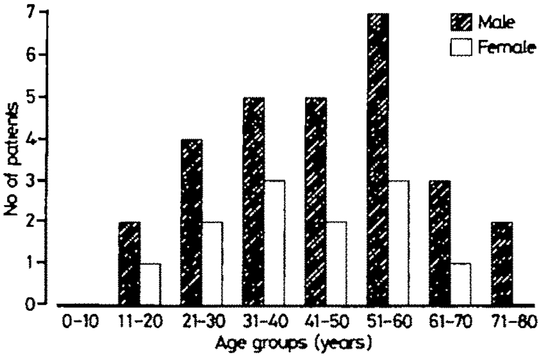

Figure *Age distribution of the 40 patients with infective endocarditis.*

ture was typical or vegetations were found on the endocardium at operation or necropsy. All patients were either referred to this centre because their clinical condition was deteriorating, usually due to congestive heart failure, or because of difficulty in the diagnosis of infective endocarditis (tertiary referral). There were 28 male and 12 female patients (male to female ratio 2·3:1). Their mean age was 44 years (range 13–79 years) (Figure).

## Results

At presentation 31 of these patients were clinically in congestive heart failure. Before infective endocarditis developed 26 patients had had rheumatic heart disease, six patients had a bicuspid aortic valve, two a ventricular septal defect, one a mitral valve prolapse, one an atrioventricular canal, and one a persistent ductus arteriosus. Three patients had no predisposing cardiac abnormality. Infective endocarditis was present in 17 patients with prosthetic heart valves; 10 patients had Starr-Edwards valves, three had Björk-Shiley prostheses, two patients had fascia lata, one a homograft, and one a Carpentier-Edwards prosthesis. In all endocarditis developed more than 60 days after the initial valve replacement. There was evidence of a predisposing event in 32 (80%) patients. Eight patients had had dental procedures within three months of presentation. The eight patients who had Q fever endocarditis had all been in contact with cattle or sheep before their illness; one of them had drunk unpasteurised milk. Seven patients had had a sore throat and five patients a respiratory tract infection. Of the remaining four, one patient had had a cholecystectomy for gall stones and had positive blood cultures for *Streptococcus faecalis*, one patient had had a toe infected with *Staphylococcus aureus* and *Staph aureus* was grown from blood cultures, one patient had had a Meckel's diverticulum removed but had negative blood cultures, while the oldest patient in the group, whose blood cultures grew *Strep faecalis* had had a recent head injury.

Causative organisms were isolated from blood cultures in only 22 (55%) patients. These were streptococci of the viridans group in nine (41%) patients, *Staph aureus* in seven (32%) patients, *Streptococcus pneumoniae* in two, *Streptococcus faecalis* in two, *Staphylococcus epidermidis* in one, and $\beta$ haemolytic streptococcus in one. None of the patients had a mixed positive culture. Eighteen (45%) patients had negative blood cultures. In 10 of these causative organisms were later identified—in eight patients serum samples were positive for chronic Q fever (*Coxiella burnetii*) and organisms were identified post mortem in two (*Staph aureus* and *Strep faecalis* were grown from the vegetations in one patient and *Candida albicans* was identified in the other).

At admission all our patients complained of fever and night sweats. Thirty five (87%) also reported malaise, weakness, headache, or tiredness. Abdominal pain was a presenting symptom in 17 (42%) patients and anorexia in 12 (30%). Eight patients complained of arthralgia and a further five (12%) patients complained of chest pain. Nine patients had symptoms from embolic episodes; most of these lesions were in the fingers and toes. Cerebral emboli, as manifest by meningeal symptoms or focal neurological deficit or both, occurred in two patients, while one other patient had a Roth spot in the fundus of the eye. The major clinical findings at presentation were hepatomegaly of 1–6 fingerbreadths in 25 patients and splenomegaly of 1–8 fingerbreadths in 22 patients. Thirteen patients had clubbing of the fingers and toes and 10 patients had purpura during the course of their illness. On routine ward testing 28 patients had haematuria.

On admission 35 of the 40 patients had a haemoglobin concentration of < 12 g/dl. Four patients had a leucopenia (white cell count < 4000/μl) and 28 patients had leucocytosis. In 37 the erythrocyte sedimentation rate was more than 20 mm an hour. Platelet counts were < 150 000/μl in 11 of the 32 patients in whom they were measured. Two of our patients, both with Q fever, had pancytopenia. A third patient with Q fever endocarditis had a normal haemoglobin concentration but pronounced reduction of the white cell and platelet counts. Gamma globulin concentration was raised in 23 of the 31 patients in whom it was measured. IgG and IgM concentrations were measured in 29 patients; they were raised in 14 and 15 patients respectively. IgA was measured in 25 patients, and it was raised in 10 of them. A latex test for rheumatoid arthritis was positive in eight of 24 patients. C3 complement was measured in 10 patients; it was raised in four, depressed in two, and normal in the remaining four.

Echocardiography was carried out in 24 patients; 18 patients had vegetations on one or several valves and in five of them blood cultures were negative—one had Q fever endocarditis and one had gram positive and gram negative organisms grown from the vegetations on the aortic valve at necropsy and one was considered to have fungal endocarditis.

Of the 31 patients in congestive heart failure at presentation two had abnormalities of the central nervous system on admission—there were signs of meningitis in one and a Roth spot in one—while in hospital four patients developed renal failure, two patients had myocardial infarction, and one had complete heart block. Ventricular fibrillation developed in two patients before operation. One patient who did not have congestive heart failure developed a transient left hemiparesis. Thus, these 40 patients were a high risk group in that throughout hospital stay only eight had no clinical evidence of congestive heart failure, renal failure, cerebral emboli, myocardial infarction, complete heart block, or ventricular fibrillation.

The duration of illness before treatment was known in 34 patients: in six it was $<1$ week, in 10 it was 1–4 weeks, in 14 it was 4–12 weeks, and in four it was $>12$ weeks. Eight patients with Q fever endocarditis were treated for $\leqslant 29$ months with oral tetracycline and co-trimoxazole or tetracycline alone.[2] The remaining 32 patients were treated for eight days to eight weeks and usually received at least two bactericidal antibiotics, depending on the bacteriological sensitivities for the organism isolated. In this group all antibiotics were given intravenously except for streptomycin which was administered intramuscularly. The empirical treatment in those patients who were culture negative was two bactericidal antibiotics, one with a maximal effect on gram negative organisms and the other with a maximal effect on gram positive organisms. These were usually benzylpenicillin and an aminoglycoside. One patient who was culture negative and who was considered to have fungal endocarditis, though this could not be proved, had six weeks' treatment with intravenous amphotericin B and oral flucytosine.

During hospital stay 16 patients (13 male) required operation because of haemodynamic deterio-

Table 1 *Details of the 12 patients who died of endocarditis*

| *No* | *Age* | *Sex* | *Organism in blood cultures* | *Presenting valve lesion* | *Prosthetic valve in situ at presentation* | *Valve replacement as emergency procedure* | *Necropsy* | *Cause of death* |
|---|---|---|---|---|---|---|---|---|
| 1 | 67 | M | Culture negative (Q fever serology positive) | Mitral incompetence | Starr-Edwards mitral | No (poor left ventricular function) | No | Congestive heart failure and renal failure |
| 2 | 79 | M | *Strep faecalis* | Aortic incompetence and mitral incompetence | None | Refused | No | Left ventricular failure and renal failure |
| 3 | 34 | F | Culture negative (*C albicans* on tricuspid valve at post mortem) | Mitral and tricuspid incompetence | Starr-Edwards mitral and tricuspid | No | Yes | Congestive heart failure and cardiogenic shock (stuck tricuspid valve) |
| 4 | 13 | M | Culture negative | Aortic incompetence (bicuspid aortic valve) | None | Yes | Yes | Left ventricular failure and myocardial infarction |
| 5 | 41 | M | *Staph albus* | Aortic incompetence | Starr-Edwards aortic | Yes | Yes | Left ventricular failure |
| 6 | 53 | M | Culture negative | Mitral incompetence | Starr-Edwards mitral | Yes | Yes | Congestive heart failure |
| 7 | 25 | F | *Staph aureus* | Aortic incompetence | Bjork-Shiley aortic | Yes | Yes | Left ventricular failure |
| 8 | 20 | F | Streptococci of the viridans group | Aortic incompetence from a prolapsed aortic valve cusp and atrioventricular canal from right atrium to left ventricle | None | No | Yes | Rupture left ventricular wall and haemopericardium |
| 9 | 76 | M | Streptococci of the viridans group | Aortic stenosis and aortic incompetence | None | No | Yes | Pulmonary embolus |
| 10 | 61 | M | *Staph aureus* | No valve lesion | Starr-Edwards aortic | No | Yes | Left ventricular failure and renal failure |
| 11 | 51 | F | Culture negative (*Strep faecalis* and *Staph aureus* grown post mortem) | Mitral stenosis and tricuspid stenosis, aortic stenosis and aortic incompetence | None | No | Yes | Congestive heart failure and renal failure |
| 12 | 63 | F | Culture negative | Mitral stenosis, aortic stenosis and aortic incompetence | None | No | Yes | Left ventricular failure |

ration (heart failure). Eleven had native valve lesions and five had prosthetic valve endocarditis. Seven of the 16 patients had emergency surgery and were pyrexial at that time. Four of the seven patients who had emergency operation died in hospital (Table 1). Only two of the 12 patients who were alive and well on discharge after operation required further operation. One patient required re-suturing of the mitral valve three years later because of a paravalvar leak, together with a saphenous vein graft to the left anterior descending coronary artery, and the other had re-operation two years later when a clotted mitral Bjork-Shiley valve was replaced with a St Jude's prosthesis.

Fifteen patients who had congestive heart failure at admission did not have operation. Six of these died in hospital (Table 1). In two patients operation was contraindicated because they had poor left ventricular function, two had advanced renal failure and congestive heart failure, one patient refused surgery, and in one patient the tricuspid valve jammed suddenly and death followed rapidly despite attempted resuscitation (Table 1). In the remaining nine patients atrial fibrillation complicated congestive heart failure. Digoxin and diuretic treatment produced a dramatic response and all these patients were out of heart failure and alive and well on discharge.

Twelve (30%) patients (seven male, five female) died in hospital (Table 1). Seven of them were >50 years old, and all deaths took place between five and 117 days of admission (mean 32 days). Half the deaths occurred in patients with prosthetic valves. Six patients had endocarditis affecting the aortic valve alone, in four it affected at least two valves, and in two patients the mitral valve only was involved. In 10 patients death was mainly the result of left ventricular or congestive heart failure. Six of the 12 patients who died were culture negative (Table 1).

Six (35%) of the 17 patients with an aortic valve lesion associated with endocarditis died, two (22%) of the nine with a mitral valve lesion died, and two (18%) of the 11 patients with aortic and mitral lesions died. Both patients with a mitral and tricuspid or mitral, tricuspid, and aortic lesion died. The remaining patient, who had a ventricular septal defect alone, survived. Two (29%) of the seven patients in whom *Staph aureus* was identified as the causative organism from blood cultures died. Six (33%) of the 18 patients with culture negative endocarditis died. However, half the patients in whom no organisms (other than those causing Q fever) were cultured died.

Both patients with myocardial infarction, one with complete heart block, four patients who developed renal failure, and two patients who developed ventricular fibrillation before operation all died in hospital. Three of the five patients with prosthetic valves who required operation because of haemodynamic deterioration during hospital stay died. Two of the four patients seen and treated more than 12 weeks from the onset of symptoms died. Both of the patients with central nervous system abnormalities at presentation survived, as did the one in whom a transient left hemiparesis developed.

Twenty eight patients were out of congestive heart failure and alive and well on discharge from hospital.

## Discussion

In the days before antibiotic treatment infective endocarditis was always fatal. Nowadays the overall mortality is reported to be approximately 30%.[3-5] Nevertheless, in a recent study only 14% of 541 patients with infective endocarditis died while in hospital.[6] This further fall in mortality is undoubtedly related to the use of early appropriate bactericidal/rickettsicidal agents and also to early cardiac valve replacement.

Despite systemic antibiotic treatment and early valve replacement the prognosis in patients with infective endocarditis remains poor, particularly for those with congestive heart failure which is now the major cause of death. In a recent review of 253 patients with infective endocarditis of native valves, low cardiac output or severe heart failure developed in 82 patients and in hospital mortality was 57%.[7] In the same series severe preoperative heart failure was present in 58 patients who had an in hospital mortality of 41%. Furthermore, mortality was 62% in patients when haemodynamic deterioration occurred in the 24 hours preceding valve replacement. The severity of the heart failure and the time between deterioration of the haemodynamic status and operation are probably the most important determinants of outcome. Twelve (30%) patients died in this series in which 31 of the 40 patients were clinically in congestive heart failure at presentation and in which 16 patients required operation during the acute phase because of haemodynamic deterioration.

It is widely accepted that there is a higher mortality among patients with coronary emboli, arrhythmias, and conduction disturbances associated with infective endocarditis. The respective mortality rates in one study were 60%, 49%, and 50%.[7] Also those with atrioventricular block, neurological complications, renal insufficiency, and those with *Staph aureus* endocarditis have been reported to have a significantly higher mortality.[6-8] In this series all patients with probable coronary emboli giving rise to myocardial infarction (two cases), with complete heart block (one case), with renal failure (four cases), and with ventricular fibrillation before operation (two cases) died. All three patients with neurological complications survived, however, and only two (29%) of the seven patients who had *Staph aureus* endocarditis, as identified by blood cultures, died.

In our study the aortic valve was the most common single site of infection (42%). This has been found by other workers.[6] In medically treated patients mortality was thought to be higher in those with infective endocarditis on the aortic valve. When valve replacement is undertaken at an opportune time, however, there is no significant difference in mortality rate between those with endocarditis of the aortic or mitral valves. In this series the mortality rate for those with infective endocarditis associated with an aortic valve lesion was 35%, for those with a mitral lesion it was 22%, and for those with aortic and mitral lesion it was 18%.

The average age of patients in this series was 44 years; the oldest patient was aged 79 years at diagnosis (Figure). An increasing incidence in the older age groups has been noted in other series, and it has been suggested that the most important factor appears to be the decreasing incidence of rheumatic heart disease and the increased longevity of the population.[6 9–11]

The ratio of males to females was 2·3:1 in this series. Others have reported a high incidence among males.[6 10 12] This increase in men is not related to the aetiology of the disease. It has been reported to be partly due to the decreasing incidence of rheumatic valvar disease, which tended to be higher in women than men, and also to the high incidence of congenital aortic valve disease, which is more common in males. Male predominance increased as infective endocarditis became a disease of older patients.[12] In our series 26 (65%) of the 40 had had previous rheumatic heart disease and 17 had prosthetic valves. McNeill *et al* found that rheumatic heart disease accounted for 75% of their patients with pre-existing heart disease,[13] whereas Schnurr *et al* noted rheumatic heart disease to be a predisposing factor in <25% of their cases.[14]

The risk of endocarditis in an individual with valvar heart disease after particular procedures or illnesses is unknown. It may depend on the age of the person, the type of valve lesion, and the type and pathogenicity of the causal organism. In our series 20% of our patients had had recent dental procedures, which are known to cause bacteraemia. There is a considerable variation in the reported incidence of dental procedures before infective endocarditis.[5] Bayliss *et al* reported that 13·7% of their cases of infective endocarditis had had dental procedures within three months of the onset of their illness.[5] All our patients with Q fever endocarditis had been in contact with animal or cattle products. In none of our patients was drug addiction a factor in the pathogenesis of endocarditis, no patients were receiving immunosuppressive drugs, and none had had infective endocarditis before.

The symptoms and signs of infective endocarditis were described by Horder in a series of 150 cases in 1909; they have remained relatively unchanged despite the availability of antibiotics.[15] Fever is the most common sign. The rise in temperature may be minimal or absent, however, especially if the patient has received antibiotics that eradicate the bacteraemia but not the disease. All our patients had pyrexia. Other signs or symptoms in our patients were similar to those noted by other workers, though their frequency varied considerably. Splenomegaly has long been considered to be an important diagnostic feature of this disease, but a greater number of our patients had hepatomegaly. This was probably due to the high incidence of congestive heart failure. Lerner and Weinstein have indicated that the incidence of clubbing has decreased; they found this sign in only 13% of their patients.[16] Its frequency (32%) in our group resembled that reported by Shinebourne *et al.*[17] Twenty two per cent of our patients had evidence of emboli, and haematuria was noted in 70% of our patients, which resembles findings reported by other workers.[10 16] It has been suggested that thrombocytopenia, as a feature of infective endocarditis, is more frequent in Q fever endocarditis than in bacterial endocarditis. Turck *et al* found thrombocytopenia in 12 of their 16 patients with Q fever endocarditis.[18] It was present in three of our eight patients. In most cases of infective endo-

Table 2 *Frequency of organisms in patients with infective endocarditis*[6 20]

| *Category* | % |
|---|---|
| Streptococci of the viridans group | 40–50% |
| Streptococci group D | 10–20% |
| *Staphylococcus aureus* | 10–15% |
| *Staphylococcus epidermidis* | 5–10% |
| Gram negative bacilli | 6–8% |
| Other microorganisms | 2–5% |
| Culture negative | 8–12% |

Table 3 *Organisms isolated in prosthetic valve endocarditis*[23]

| *Category* | % |
|---|---|
| Staphylococci | 37% |
| Streptococci | 20% |
| Gram negative organisms | 13% |
| Fungi | 9% |
| Mixed infections | 21% |

carditis there is a polyclonal immunoglobulinopathy, with high concentrations of IgG, IgM, IgA, and rheumatoid factors have been noted in 43% to 85% of patients with infective endocarditis.

Vegetations are detected by ultrasound in 13% to 78% cases of endocarditis.[19] When heart failure follows valve destruction, however, large vegetations are often seen. Seventy five per cent of the 24 patients in the study who were examined by echocardiography were positive for this sign. But the technique is limited if the duration of symptoms is short and in the presence of calcified or prosthetic valves (which are echo dense) when identification of echoes caused by vegetations is difficult.

Although the type of organisms giving rise to infective endocarditis has changed in the past decade, streptococci remain the largest group of organisms (Table 2). The incidence of culture negative infective endocarditis varies markedly from series to series and has been reported to be as low as 3% and as high as 64%.[21 22] In recent years the percentage of culture negative endocarditis patients has fallen. This was thought to be due to improved culture techniques. Pesanti and Smith, however, reported that patients with infective endocarditis and negative blood cultures were twice as likely to have clinically evident congestive heart failure and major embolic episodes on admission than patients with positive blood cultures.[21] Also, such patients were more likely to be on antibiotic treatment before culture. Case selection may also reduce the frequency of culture negative infective endocarditis. Pesanti and Smith found unusual organisms only occasionally; most patients were infected with common organisms, or organisms were no longer evident within the vegetations.[21] Thus, one group has suggested that many cases of culture negative infective endocarditis represent an immunological, rather than an infectious disease, that is one which is triggered by an infectious agent. The immediate mortality of patients with culture negative infective endocarditis was higher than that of patients with culture positive disease and was comparable to that seen in staphylococcal or prosthetic valve endocarditis.[21] Six (33%) patients in our series of 18 with culture negative endocarditis died. When those with Q fever endocarditis were excluded, however, five (50%) of 10 died.

Table 3 shows the infecting organisms found in a reported study of prosthetic valve endocarditis. In early prosthetic valve endocarditis, however, the incidence of staphylococci, gram negative pathogens, and fungi has been reported to be significantly higher.[23] Of 17 cases of late prosthetic valve endocarditis eight (47%) infections were due to streptococci, four (24%) to staphylococci, and 5 (29%) to mixed infection.[23] In another series of late prosthetic valve endocarditis a similar incidence was reported with 31 causative organisms identified in 29 cases; 15 (48%) cases were due to streptococci, 11 (35%) to staphylococci, and five to other species.[24] In our series of 17 patients with late prosthetic valve endocarditis, 14 had causative organisms identified by culture or serology or at necropsy. Six (43%) patients had Q fever endocarditis, four (29%) had staphylococci, three (21%) had streptococci, and one (7%) had *C albicans*. Aortic prosthetic valve endocarditis is reported to be 1·6 times more common than mitral prosthetic valve endocarditis.[23] Infective endocarditis is more common in multiple valve replacement than in isolated valve replacements. Seven of the 17 patients in our study with prosthetic valve endocarditis had an aortic prosthesis, five had a mitral prosthesis, and five had either mitral and aortic (four cases) or mitral and tricuspid prostheses (one case). The mortality rate for late prosthetic valve endocarditis can reach 45%.[23] In our series six (35%) of 17 patients with prosthetic valves died, but three of the five with prosthetic valves in whom haemodynamic deterioration led to a further operation while they were in hospital died. Apparently the two factors with the greatest influence on the prognosis in patients with prosthetic valve endocarditis are the infecting organism and the degree of cardiac dysfunction.[25]

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# Sudden death and vigorous exercise—a study of 60 deaths associated with squash

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SUMMARY The circumstances surrounding 60 sudden deaths (59 men, one woman) associated with squash playing are described. The mean age (SD) of those who died was 46 (10·3) years (range 22–66 years). Necropsy reports were available in 51. The certified cause of death was coronary artery disease in 51 cases, valvar heart disease in four, cardiac arrhythmia in two cases, and hypertrophic cardiomyopathy in one case. There were only two deaths from non-cardiac causes. Forty five of those who died had reported prodromal symptoms, the most common of which was chest pain, and 22 were known to have had at least one medical condition related to the cardiovascular system during life, the most common of which was systemic hypertension (14 subjects). Those dying from coronary artery disease had a high frequency of risk factors.

Some of these deaths might have been prevented by appropriate counselling of players after prospective medical screening, which would have detected most of the patients with overt cardiovascular disease and some of those with subclinical coronary artery disease.

The Squash Rackets Association have estimated that there may be 2·5 million people in the United Kingdom playing squash once or more a month. Squash is particularly popular with middle aged male executives and competitions have recently been expanded to include veteran and even vintage groups. Therefore a growing number of high risk individuals are being exposed to the potential hazards of a physically exhausting sport. Most previous investigation of sudden death in sport has concentrated on running[1-3] and track and field sports.[4-7] In 1984 we reported on 30 deaths associated with squash.[8] We have continued to collate information on sudden death in squash players and we now have information on 30 additional deaths.

## Subjects and methods

Because sudden death associated with sport or vigorous exercise is normally categorised only by medical cause of death it is usually not possible to obtain retrospective information on such cases. We were able to collate a series of 89 sudden deaths associated with squash that occurred between October 1976 and February 1984 by examining press reports and by a prospective mail survey of sports centres and squash clubs throughout the United Kingdom. The Squash Rackets Association assisted us with several cases, and a few were reported directly to us by witnesses or by officials of individual squash clubs. In 60 cases we obtained sufficient information to investigate the death in detail. In each of these cases the next of kin (usually the spouse) completed a detailed questionnaire to establish the circumstances surrounding the sudden death and the presence of premorbid symptoms or risk factors for coronary artery disease, as defined by Kannel *et al.*[9] Prodromal symptoms were defined as any change from usual health status considered to be important by the subject and reported to relatives or friends within one week of death.[10] Next of kin were invited to provide a crude assessment of the level of fitness and personality characteristics of the deceased subject. We sought permission to approach witnesses to the event and the family physician. In addition if the subject had undergone a medical examination for the purposes of employment or life insurance we asked permission to approach the appropriate authority for the results. Necropsy findings (if available) were reviewed and the results of any coroner's enquiry (England) or investigation by a procurator fiscal (Scotland) were taken into account.

Coronary artery disease was diagnosed when there

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Accepted for publication 4 November 1985

was necropsy evidence of severe or pronounced coronary atherosclerosis (as judged by the pathologist) or when the lumen was narrowed by more than 70% with or without evidence of fresh thrombus and in the absence of other abnormalities. Pathological evidence of a healed myocardial infarction was taken to support a diagnosis of coronary artery disease.

## Results

We identified 60 cases of sudden death associated with squash. They all occurred in the United Kingdom between May 1976 and April 1984. Only one of the 60 cases was female and all subjects were white. Their mean age (SD) was 46 (10·3) years (range 22–66 years). The Figure shows the distribution of ages.

Sudden death has been defined as death occurring within 1–24 hours of the onset of symptoms.[11 12] In this study all subjects collapsed while playing squash or within an hour of playing, and all except one died within an hour of play. The remaining subject died in hospital six hours after playing. With this exception the onset of symptoms was rapid, and culminated in collapse and unconsciousness. Forty six subjects collapsed on the squash court—10 of these in the first 10 minutes of play (mean (SD) of 23 (12) minutes into play) and 14 collapsed in the first hour after play. Nine of these subjects collapsed in the first 10 minutes after exercise. Four subjects collapsed while taking a hot shower. Death was instantaneous in 59 cases—the remaining subject collapsed 60 minutes after play, while driving, and died six hours later in hospital. Cardiopulmonary resuscitation was attempted in 46 cases, usually by onlookers many of whom were physicians, nurses, or first aid personnel, but defibrillation was carried out in only one case.

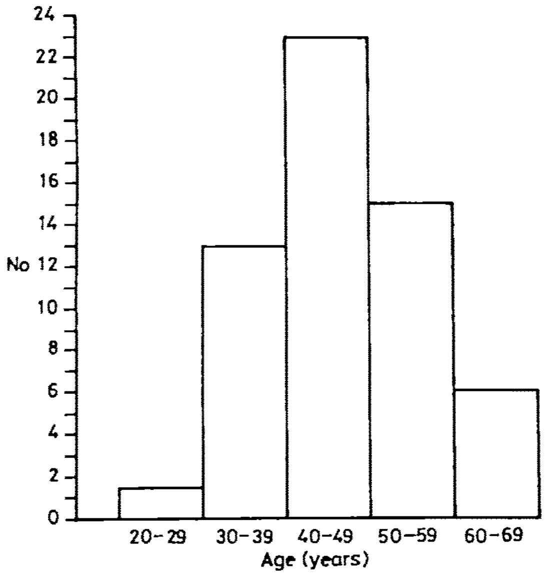

Figure *Age distribution of sudden deaths associated with squash.*

All the subjects had been playing squash for at least one year (mean 12 (9·7) years; range 1–40 years). In nine subjects we could not accurately determine the frequency of participation. Of the remainder, 48 players visited the court on a mean of 2·3 (1·48) times a week (range 0·25–7 times per week) to play squash and they usually played for 40–60 minutes. One subject had, on medical advice, not played squash for five years, another played only when on holiday, and one subject (aged 60 years) had recently started playing with his son after a 10 year break after medical advice to retire from the game. Sixteen subjects had started to play squash when they were over the age of 40, whereas only 17 had been playing before the age of 30 years.

### CAUSE OF DEATH

Table 1 summarises the probable causes of death. Necropsy reports were available in 51 cases. Coronary artery disease was confirmed as the cause of death in 42 cases in which there was severe or pronounced stenosis of at least one main coronary artery. Although 18 subjects had pathological evidence of a healed myocardial infarction, this had been diagnosed in only two cases during life. In a further two cases, however, there had been clear symptoms of prolonged anterior chest pain 10 days and four months before death. In both of these cases the pathological appearances were compatible with a myocardial infarction at these times.

In 35 cases dying of coronary artery disease a detailed description of the state of the coronary arteries was available from the necropsy report. The left anterior descending coronary artery was the single artery most often affected by atherosclerosis. There was severe triple vessel disease in 12 cases. Fresh thrombus occluded a coronary artery in nine cases. In one case (aged 22 years) the left main stem coronary artery was completely occluded by fresh thrombus in the absence of important coronary atheroma.

Table 1 *Probable cause of death in 60 squash players*

| *Cause* | *No* |
|---|---|
| Coronary artery disease | 51 |
| Valvar heart disease | 4 |
| Cardiac arrhythmia | 2 |
| Non-cardiac | 2 |
| Hypertrophic cardiomyopathy | 1 |

Valvar heart disease that had been diagnosed during life caused death in four cases; none of them had been advised against physically exhausting sporting activity. At necropsy one subject (aged 26 years) with a congenitally stenotic bicuspid aortic valve was also found to have concentric left ventricular hypertrophy and irregular thickening of the valve cusps and distortion of the commisures. Another subject had congenital prolapse of the mitral valve with atrial fibrillation during life—this abnormality was confirmed at necropsy and was accompanied by pronounced left ventricular hypertrophy (heart weight 550 g) in the absence of important coronary artery disease. The cause of death was certified as acute heart failure, possibly associated with a cardiac arrhythmia.[13] Mitral stenosis resulting in acute heart failure was found in the second subject in the absence of important coronary artery disease. The fourth subject had a calcified aortic valve, resulting in severe aortic stenosis, and calcified coronary arteries. The certifying pathologist judged that the aortic valve lesion was the principal cause of death.

In one subject hypertrophic obstructive cardiomyopathy, a disorder known to be associated with sudden death during strenuous exercise,[14] was found in the absence of other abnormalities. His family physician was not aware that he had this disorder, and annual medical examinations at work had detected no abnormality. In only two cases was death the result of non-cardiac causes. One case had a right intracranial haemorrhage, and symptoms developed 60 minutes after this subject had finished playing squash. He died in hospital 6 hours later without regaining consciousness. The other subject had played squash soon after a heavy meal and at necropsy both lungs were found to be collapsed as a result of aspiration of stomach contents. There was no evidence of heart disease in either case. In two cases, no abnormality was found at necropsy and the certifying pathologist judged that death in both had resulted from a cardiac arrhythmia. This diagnosis should ideally be supported by a thorough histopathological examination of the conduction system of the heart.[15] This was carried out in a specialist centre in one case, but no abnormality was detected. Since both deaths were instantaneous it seems likely that the certified cause of death was correct.

All of the nine cases in which necropsy was not performed were certified as having died of coronary artery disease. In five cases there were no clearly distinguishable features apart from the sudden collapse to support this diagnosis. Thirty minutes before death one subject complained of cardiac pain to his physician. Since this was accompanied by sweating, coronary artery disease was likely to have been the cause of death. Two subjects had a history of previous myocardial infarction and one of these had also had documented aortic regurgitation in the 10 years before death. A further subject had a history of angina pectoris one year before death and had important ST segment depression on exercise electrocardiography. In each of these nine cases the certifying doctor judged that coronary artery disease was the cause of death.

### PREMORBID CONDITIONS AND SYMPTOMS

Forty five subjects had reported at least one prodromal symptom within one week of their sudden death, and 16 subjects had reported more than one symptom (Table 2). Only nine were known to have consulted their family physician about these symptoms, although a further two had arranged appointments with their practitioner.

Twenty two subjects were known to have had at least one medical disorder during life related to the cardiovascular system; 14 had hypertension documented on two or more occasions. Only two subjects, however had been on antihypertensive medication. Excluding hypertension, 14 subjects had medical conditions known to themselves and their family physician that were relevant to the cardiovascular system (Table 3).

Of the 51 subjects dying of coronary artery disease, 32 had at least one risk factor, 15 had two, and five had three or more (Table 4).

### PERCEPTION OF PHYSICAL FITNESS

Next of kin were requested to assess the physical fitness of the deceased in relation to the general population in five categories ranging from very fit to very unfit. No subject was considered to be unfit, whereas 32 of the group were considered to be very fit, 22 fit, and only six were considered to be of average fitness.

Table 2 *Prodromal symptoms*

| *Symptom* | *No* |
|---|---|
| Chest pain/angina | 15* |
| Increasing fatigue | 12 |
| Indigestion/heart burn/gastrointestinal symptoms | 10 |
| Excessive breathlessness | 6† |
| Ear or neck pain | 5 |
| Vague malaise | 5 |
| Upper respiratory tract infection | 4 |
| Dizziness/palpitation | 3 |
| Severe headache | 2‡ |
| None | 5 |

*One subject, an international squash player, had recently consulted a physician because of chest pain after squash play.

†One subject, who ran one mile every morning, was extremely breathless on three successive mornings before he died, but was not deterred from further strenuous exertion

‡Cause of death in one subject was intracranial haemorrhage.

Table 3 *Clinical and demographic findings in subjects known to have medical conditions*

| *Subject* | *Age* | *Years playing squash* | *Frequency* | *Clinical diagnosis* | *Symptoms* | *Risk factors* | *Cardiac pathology* |
|---|---|---|---|---|---|---|---|
| 1 | 52 | 5 | 1 | Two previous myocardial infarctions, MODM | Nocturnal angina | Diabetes | Healed myocardial infarction, R + L CA occlusion |
| 2 | 69 | 35 | 2 | IHD, previous CABG, internal pacemaker | General malaise | Smoking | Healed myocardial infarction, 3-vessel disease |
| 3 | 26 | 3 | 1 | Aortic stenosis | Flu-like symptoms 1 week | — | Bicuspid aortic valve, concentric LV hypertrophy |
| 4 | 65 | 35 | 1st match in 5 years | Previous myocardial infarction | Fatigue | Smoking, hypertension | Not available |
| 5 | 44 | 3 | 2–4 | IHD | Angina pectoris | Smoking, family history | 3-vessel disease, thrombus occluding RCA |
| 6 | 51 | 25 | 3–4 | Atypical chest pain | Chest pain | Family history | Healed myocardial infarction, 3-vessel disease |
| 7 | 43 | 2 | 2 | Gastritis | Dyspepsia, chest pain, malaise | — | Myocardial infarction, 10 days old, LV hypertrophy, 3-vessel disease |
| 8 | 62 | 30 | 3 | Atrial fibrillation | Previous collapse at squash, malaise | — | Healed myocardial infarction, 3-vessel disease |
| 9 | 39 | 10 | 7 | Subarachnoid haemorrhage 17 yr |  | Smoking | LAD occlusion |
| 10 | 54 | 2 | 1–2 | IHD | Angina pectoris | Smoking, hyperlipidaemia | Not available |
| 11 | 66 | Return after 10 year lay-off | 1–2 | Atrial fibrillation mitral valve prolapse | Dyspnoea | Family history | Mitral valve prolapse large dilated heart (550 g) |
| 12 | 32 | 6 | 1 | Previous myocardial infarction, aortic incompetence | — | Smoking, hyperlipidaemia, hypertension | — |
| 13 | 45 | 12 | 3–4 | Mitral stenosis | — | Family history | LV hypertrophy, severe mitral stenosis, moderate CHD |
| 14 | 52 | 4 | 3 | Two previous myocardial infarctions, MODM | — | Smoking, hypertension, diabetes | — |

CABG, coronary artery bypass graft; IHD, ischaemic heart disease; L, left; LAD, left anterior descending coronary artery, LV, left ventricule; MODM, maturity onset diabetes mellitus, R, right.

### PERSONALITY AND PSYCHOLOGICAL INFLUENCES

Many players had clearly ignored prodromal symptoms and known medical conditions and had continued to play squash. Next of kin were asked to describe the deceased's predominant personality characteristics. Twelve subjects were considered to be competitive, ambitious, hard driving, and perfectionist, 13 were thought to be very aggressive, two to be very competitive, and one to be obsessive about fitness. One subject was described as eccentric. Only four were thought to be passive. In 27 no clearly recognisable traits could be identified.

Table 4 *Risk factors for coronary heart disease in 51 subjects dying of coronary heart disease*

| *Risk factor* | *No* |
|---|---|
| Smoking (> 10 cigarettes/day) | 25 |
| Family history of early myocardial infarction (< 55 years) | 18 |
| Hypertension | 14 |
| Angina/previous myocardial infarction | 8 |
| Hypercholesterolaemia | 3 |
| Diabetes mellitus | 2 |

Psychological or emotional stress might have contributed to death in four cases. The most extreme case was that of a man of 26 with a congenitally stenotic aortic valve who collapsed and died on the court minutes after breaking his opponent's jaw.

### OCCUPATION

Many of the people in this study had professional or executive jobs. Fourteen were company directors, nine worked in higher education (two university professors and seven lecturers), four were civil servants, one was a physician, four were engineers, and one was a school teacher. The remainder worked in various other occupations only two of which would be regarded as non-sedentary.

## Discussion

These data confirm that coronary artery disease is responsible for most cases of sudden death associated with vigorous sport. The results in the age group of subjects that we studied accord with those of other studies that examined sudden death in sport.[1-5] In particular, a recent study of 30 deaths in joggers reported a similar frequency of coronary artery disease and necropsy evidence of healed or acute myocardial infarction.[3] The authors of this report also remarked on the high frequency of coronary artery disease risk factors in their group. Another study of nine joggers demonstrated a high frequency of premorbid cardiovascular conditions (that is previous myocardial infarction, angina, hypertension, diabetes),[16] in keeping with our results, and the authors suggested that the deaths might have been delayed had the subjects participated in less strenuous exercise. Hypertrophic obstructive cardiomyopathy may be responsible for about half the sudden deaths in a youthful athletic population during sport,[17] but we identified only one such case (aged 38 years). Less common causes of sudden death during physical activity have been described, including myocarditis[18] and fibromuscular dysplasia of the sinus or atrioventricular node artery.[15] Such abnormalities might be missed during routine necropsy examination.[19] In two of our cases no gross pathological abnormality was found to explain the sudden death, in one of these cases a detailed histopathological examination performed at a special centre showed no abnormality. The cause of death in these cases is a matter for speculation, although a cardiac arrhythmia seems to be the most likely cause of death.

The most frequent pathological lesion was severe stenosis of at least one major coronary artery; a fresh occlusive thrombus was present in only 18% of cases. A recent study of 100 sudden cardiac deaths by Davies and Thomas, showed that 44% of cases had major fresh thrombus occluding more than 50% of the cross sectional area of the coronary vessels.[20] In our study the coroner's routine necropsy may not have detected thrombi that would have been found by a prospective detailed study of coronary vasculature. Alternatively, it is possible that coronary artery occlusion can occur without thrombus formation during vigorous exercise, perhaps as a result of coronary artery spasm.

Sudden cardiac death is usually caused by ventricular fibrillation or asystole. Such events may be more likely during vigorous exercise in subjects with coronary artery disease, because oxygen demand may outstrip the ability of the coronary arteries to supply it. It is also possible that metabolic influences associated with exercise may precipitate or contribute to an arrhythmia. For example, free fatty acid and catecholamine concentrations may rise during exercise[21] and this can cause arrhythmias[22] and arterial thrombosis[23] especially in the presence of coronary artery stenosis.[24] These changes, together with exercise-induced lactic acidosis,[25] and hyperkalemia[26] may also help to explain the failure of cardiopulmonary resuscitation. In this study we were impressed by the large number of cases in which cardiopulmonary resuscitation had been attempted by trained personnel, and, as we have no data on survivors, this leads us to suspect an underestimation of the frequency of cardiac events during squash.

We cannot say whether these subjects would have survived for longer if they had not exercised so vigorously. We suspect, however, that myocardial infarction is more likely to cause sudden death when it occurs during vigorous exercise. This suggestion is supported by the Framingham study[27] and by a British report examining the circumstances surrounding 100 sudden deaths from coronary artery disease.[28] Friedman *et al* found that individuals dying instantly, as in this study, were significantly more likely to have been engaging in severe or moderate exertion just before death and usually had severe coronary artery disease which precipitated cardiac arrhythmias.[12] We have previously demonstrated that squash is capable of raising heart rate to 90% of predicted maximum for extended periods and of generating important cardiac arrhythmias in a young normal population.[29] This may indicate that squash is an inappropriate sport for those with coronary artery disease or other cardiac disease or even those whose age puts them at increased risk of coronary disease.

Many individuals in this study with known medical conditions continued to play squash. Men in middle age seem reluctant to acknowledge that they may be in poor physical condition or health. We[8] and others[24] have noted that sportsmen tend to deny physical infirmity and prodromal symptoms. In this study 22 subjects had known cardiovascular disease and 75% had complained of at least one prodromal symptom but apparently had not sought medical advice. These people may not have recognised the importance of their symptoms. People with recognised cardiovascular disease should be warned by their physicians not to take part in vigorous physically exhausting exercise although more gentle exercise may be beneficial.

In addition to a tendency to ignore prodromal symptoms and pre-existing disease at least half of the subjects in this series may have been type A personalities, and this in itself may have increased their risk of sudden death and the development of coronary heart disease.[30 31] Acute psychological stress, which both Engel[32] and Lown[33] believe can precipitate lethal cardiac arrhythmias, was present in four cases. The mechanism by which type A behaviour contributes to sudden death is unknown.

Although the risk of sudden death during squash is small the number of deaths associated with the game is appreciable. Although this may merely reflect the popularity of the game it is just as likely to reflect its strenuous and demanding nature, which clearly makes it unsuitable for those with cardiovascular disease. The preponderance of men in this study may indicate their greater participation in the sport at an age when they are at increased risk of coronary artery disease.

It is not our object to condemn squash as a recreation, rather we aim to draw attention to areas in which its safety may be improved and with it the enjoyment of playing. We congratulate the Squash Rackets Association for forming a medical study group in 1980 to monitor the situation and for circulating a list of precautions to prospective players in all their affiliated clubs.

We hope that reports such as this one will increase the awareness of both the public and the medical profession of the dangers of exhausting exercise in unsuitable subjects.

We thank the Squash Rackets Association, the Coroners Society (England), and Crown Office (Scotland) for their help in collation of data; and the relatives and general practitioners for their cooperation. The study was supported by a grant from the Chest, Heart and Stroke Association.

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# Effect of parasympathetic impairment on the haemodynamic response to handgrip in Chagas's heart disease

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SUMMARY Haemodynamic responses to sustained isometric exercise (handgrip at 30% of maximum voluntary capacity) were studied in 10 patients with Chagas's cardiopathy without previous or current heart failure. Five of the patients (group 1) had profound impairment of parasympathetic control of heart rate. They had no tachycardia in response to intravenous administration of atropine and no bradycardia during phase IV of the Valsalva manoeuvre. The other five (group 2) showed normal vagal regulation of heart rate, as judged by chronotropic responses to these tests.

The heart rate change (mean (SD)) elicited by the handgrip test was significantly lower in group 1 (from 93·0 (14·1) to 95·0 (16·7) beats/min) than in group 2 (from 78·2 (15·8) to 92·8 (18·1) beats/min). Pressor responses to handgrip were of similar magnitude (from 91·6 (7·8) to 109·0 (8·0) mm Hg in group 1 and from 88·6 (11·9) to 106·8 (20·9) mm Hg in group 2). In both groups no significant change in stroke index was detected during handgrip. Cardiac index increased during handgrip from 4·0 (1·2) to 4·8 (1·3) $1/min/m^2$ in group 2, but there was no significant change in group 1 (from 4·9 (0·7) to 4·8 (1·1) $1/min/m^2$). Changes in calculated systemic vascular resistance were significantly higher in group 1 (from 934 (175) to 1176 (383) dyn s $cm^{-5}$) than in group 2 (from 1109 (404) to 1112 (424).

This study shows that parasympathetic impairment adversely influences the haemodynamic pattern of response to isometric exercise in patients with Chagas's heart disease. In such conditions, the pressor response to handgrip is predominantly mediated by an increase in systemic vascular resistance rather than an increase in cardiac output.

In normal subjects sustained isometric muscular contractions produce significant increases in heart rate, cardiac output, and systemic arterial pressure.[1-5] The increase in cardiac output elicited by isometric exercise is dependent upon the concomitant chronotropic response, since no detectable change in stroke volume is usually seen during this kind of effort.[1 6 7] On the other hand, the rise in arterial pressure is directly proportional to the increase in cardiac output, with no appreciable change occurring in calculated systemic vascular resistance.[5 7]

Parasympathetic withdrawal is the efferent mechanism responsible for the initial rise in heart rate that occurs in response to isometric exercise.[3 7-11] Although it has not been identified in some studies,[8 12] sympathetic stimulation makes a later contribution to the chronotropic response; the adrenergic mechanism has been detected as early as 10 seconds after the beginning of handgrip exercise at 75% of maximum voluntary capacity,[11] and after 30 seconds of isometric exercise at 30% of maximum voluntary capacity.[7]

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Accepted for publication 14 September 1985

Isometric exercise has been used to evaluate the chronotropic effects on cardiac grafts[13] and for the assessment of autonomic disturbances in diseases such as hypertension,[14] diabetes mellitus,[15-17] and congestive cardiomyopathy.[18] No studies, however, have been carried out to assess the overall haemodynamic consequences of impaired cardiovascular responses to isometric exercise in diseases in which there is a primary autonomic disturbance.

Chagas's disease is well known for its unique involvement of the cardiac parasympathetic system in the absence of myocardial failure.[19-25] We have evaluated haemodynamic performance during isometric exercise in chagasic patients known to have parasympathetic impairment of heart rate control, and we have compared their responses with those of chagasic patients without impaired autonomic control.

## Patients and methods

### PATIENTS

The study was performed in 10 selected male patients with chronic Chagas's heart disease, after they had given their written consent and the study had been approved by the hospital. All had positive complement fixation tests and the electrocardiographic changes typical of heart involvement in Chagas's disease. No patient was in heart failure or had a history of heart failure. Patients were selected on the basis of their response to an intravenous injection of atropine (0·04 mg/kg body weight) given at the rate of 1 mg/min, while the patient was supine. We selected five patients (aged 19–44, mean 30 years) in whom the heart rate did not increase after atropine (group 1), and five patients (aged 30–46, mean 38) in whom there was the expected tachycardia in response to atropine (group 2). There was slight cardiomegaly (transverse cardiothoracic index 0·51–0·53) in four patients in group 1, who also showed clinical signs of megaoesophagus or megacolon or both. This kind of chagasic involvement of hollow viscera was also diagnosed in four patients in group 2. Four patients in group 1 and three in group 2 were in class II of the New York Heart Association criteria (1973) and the others were in class I. All patients were in sinus rhythm, and none was on any drugs capable of interfering with cardiac function. Clinical hypertension was also excluded in every case.

## Methods

Each patient was first familiarised with the calibrated spring-type handgrip dynamometer and the maximum voluntary instantaneous contraction of the dominant arm was determined. After local anaesthesia, a Cournand 7F cardiac catheter was introduced by cutdown into the contralateral basilic vein, and advanced under fluoroscopic control to the right atrium. A 19 G indwelling Cournand needle was placed in the right femoral artery by percutaneous puncture under local anaesthesia.

A standard lead of the electrocardiogram, the systemic arterial pressure, and respiratory chest motions were continuously monitored and recorded in a MR-105 Waters Polygraph. The zero reference level was set in the mid-chest anteroposterior position at the third intercostal space for the P23 Gb Statham strain-gauge manometer. The respiratory cycles were recorded through a pneumograph belt connected to a P23 AA Statham strain-gauge that was also used for measuring oral pressure during the Valsalva manoeuvre. Dilution curves were determined by injection of 5 mg of indocyanine green dye into the right atrium and continuous sampling of arterial blood through a Waters fast dynamic response densitometer. Cardiac output was determined by the Hamilton method, after

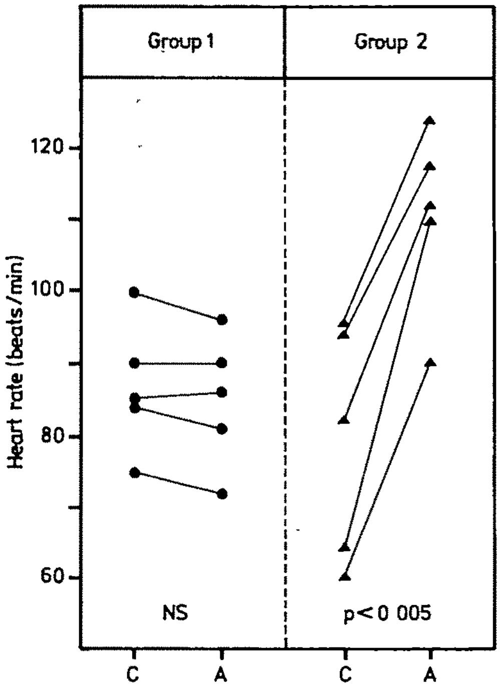

Fig. 1 *Effect of intravenous atropine (0·04 mg/kg body weight) on resting heart rate of patients with chagasic myocarditis. Only group 2 patients showed tachycardia after atropinisation (A). (C) control values.* $p < 0\,005$*, Student's t test for paired samples. NS, not significant.*

Table 1 *Systemic arterial pressure (systolic and diastolic, mm Hg) and heart rate (beats/min) during baseline and the strain and recovery phases of Valsalva manoeuvre in chagasic patients with (group 1) and without parasympathetic impairment (group 2)*

| *Case* | *Baseline* | | *Strain* | | *Recovery* | |
|---|---|---|---|---|---|---|
| | *SAP* | *HR* | *SAP* | *HR* | *SAP* | *HR* |
| Group 1: | | | | | | |
| 1 | 140/70 | 70 | 115/77 | 85 | 180/95 | 81 |
| 2 | 120/80 | 114 | 100/80 | 123 | 160/105 | 120 |
| 3 | 122/74 | 94 | 98/70 | 108 | 180/110 | 100 |
| 4 | 150/84 | 90 | 120/84 | 110 | 220/125 | 105 |
| 5 | 135/75 | 96 | 110/72 | 100 | 172/96 | 96 |
| Group 2: | | | | | | |
| 6 | 120/60 | 84 | 100/70 | 96 | 205/90 | 60 |
| 7 | 150/70 | 54 | 115/70 | 75 | 190/90 | 50 |
| 8 | 135/65 | 107 | 100/75 | 125 | 185/90 | 83 |
| 9 | 127/65 | 81 | 95/65 | 114 | 200/90 | 64 |
| 10 | 152/90 | 84 | 115/90 | 120 | 180/115 | 78 |

SAP, systemic arterial pressure (mm Hg), HR, heart rate (beats/min).

calibration of the densitometer with known concentrations of dye in blood samples of each patient.

The studies were carried out in a temperature-regulated room (22–24°C) with the patients either fasting or in the postabsorptive state after a light meal.

The experimental protocol started with each patient performing a standard Valsalva manoeuvre; the oral pressure was raised suddenly to 40 mm Hg and kept constant for about 20 seconds. Continuous recording of electrocardiogram, systemic blood pressure, and oral pressure was obtained before, during strain, and 20 seconds after release of the strain.

Five minutes after the end of the standard test baseline recordings were obtained and then the patients performed a sustained handgrip at 30% of maximum voluntary capacity for two minutes. In the last half of the exercise period, dilution curves were again obtained, and arterial pressure was immediately measured. We made certain that patients maintained normal respiration during exercise, so that inadventent performance of the Valsalva manoeuvre was avoided.

Heart rate was counted for intervals of 10 seconds during the recording of dilution curves in the baseline and handgrip periods, as well as before, during, and after the Valsalva manoeuvre. Mean systemic arterial pressure (MSAP) was recorded by electronic damping of pulse contours. Systemic vascular resistance (SVR) was derived from the formula—SVR = MSAP × 80/cardiac output.

### STATISTICAL ANALYSIS

Values of variables measured during handgrip were compared with baseline values in each group by Student's paired *t* test. The statistical significance of differences in changes evoked by handgrip, between the two groups, was assessed by unpaired Student's *t* test. P values <0·05 were regarded as significant.

## Results

### CHRONOTROPIC RESPONSES TO ATROPINE

Fig. 1 shows that in all patients in group 1 heart rate did not increase in response to atropine (individual changes were −3, −4, +1, −3, and 0 beats/min). In group 2 patients atropine induced pronounced tachycardia in all cases (individual changes were +46, +30, +28, +30, and +24 beats/min).

Table 2 *Haemodynamic variables at rest and during the second minute of isometric exercise in chagasic patients with (group 1) and without parasympathetic impairment (group 2)*

| *Case* | *At rest* | | | | |
|---|---|---|---|---|---|
| | *HR (beats/min)* | *MSAP (mm Hg)* | *CI ($l/min/m^2$)* | *SVI ($ml/m^2$)* | *SVR ($dyn\ s\ cm^{-5}$)* |
| Group 1: | | | | | |
| 1 | 75 | 90 | 3·9 | 51·9 | 1199 |
| 2 | 114 | 88 | 4·5 | 41·0 | 899 |
| 3 | 90 | 90 | 4·9 | 54·5 | 875 |
| 4 | 90 | 105 | 5·4 | 60·0 | 978 |
| 5 | 96 | 85 | 5·8 | 60·7 | 719 |
| Mean (SD) | 93·0 (14·1) | 91·6 (7·8) | 4·9 (0·7) | 53·6 (8·0) | 934 (175) |
| Group 2: | | | | | |
| 6 | 66 | 73 | 2·6 | 40·0 | 1221 |
| 7 | 60 | 98 | 4·3 | 72·0 | 1060 |
| 8 | 100 | 80 | 5·2 | 52·0 | 733 |
| 9 | 84 | 90 | 5·1 | 60·8 | 793 |
| 10 | 81 | 101 | 2·8 | 35·0 | 1738 |
| Mean (SD) | 78·2 (15·8) | 88·6 (11·9) | 4·0 (1·2) | 52·0 (15·1) | 1109 (404) |

*Mean values of variables measured during the second minute of isometric exercise that are significantly ($p<0·05$) different from those at rest (Student's *t* test for paired values). HR, heart rate; MSAP, mean systemic arterial pressure; CI, cardiac index; SVI, stroke volume index; SVR, systemic vascular resistance.

### HEART RATE AND BLOOD PRESSURE RESPONSES DURING THE VALSALVA MANOEUVRE

Table 1 shows that in both groups there was a pronounced overshoot in blood pressure after the release of the strain. Only patients in group 2, however, had a prompt reflex bradycardia occurring in the first 20 seconds after the end of the strain. Patients in group 1 did not show cardiac slowing below baseline heart rate in the first 20 seconds after the Valsalva manoeuvre.

### HAEMODYNAMIC RESPONSES TO ISOMETRIC EXERCISE

Table 2 shows that handgrip at 30% of maximal voluntary capacity induced a significant increase in mean (SD) heart rate in group 2 only (from 78·2 (15·8) to 92·8 (18·1) beats/minute (+ 18·7%, $p < 0·05$)). There was a similar increase in systemic arterial pressure in both groups (from 91·6 (7·8) to 109·0 (8·0) mm Hg (+ 19·0%, $p < 0·001$) in group 1 and from 88·6 (11·9) to 106·8 (20·9) mm Hg (+ 20·5%, $p < 0·05$) in group 2).

In group 1 there was no significant change in the mean cardiac index. In group 2 cardiac index rose from 4·0 (1·2) to 4·8 (1·3) l/min/m$^2$ (+ 20·0%, $p < 0·005$). No significant changes in stroke volume index were found in either group. In contrast, the calculated systemic vascular resistance was higher during handgrip than at baseline in group 1 (from 934 (175) to 1176 (383) dyn s cm$^{-5}$) (+ 25·9%, $p < 0·025$) but not in group 2.

Fig. 2 shows the changes in heart rate, systemic arterial pressure, cardiac index, and systemic vascular resistance that were elicited by handgrip. Group 2 patients showed significantly greater ($p < 0·05$) increases in heart rate and cardiac index than patients in group 1. Increases of mean blood pressure were similar in both groups, whereas changes in systemic vascular resistance were significantly higher in group 1 ($p < 0·05$).

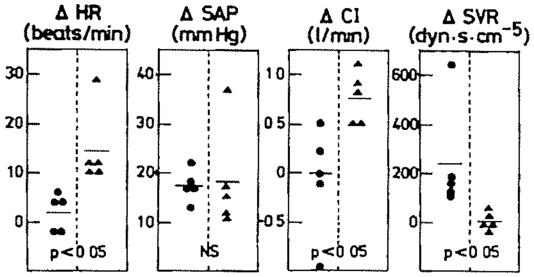

Fig. 2 *Changes in heart rate (ΔHR), mean systemic arterial pressure (ΔSAP), cardiac index (ΔCI), and systemic vascular resistance (ΔSVR) evoked by handgrip at 30% of maximal voluntary capacity in chagasic patients with (circles) and without parasympathetic impairment (triangles). Statistical significance was assessed by Student's t test for unpaired samples.*

## Discussion

These results clearly show that there is a distinctive pattern of haemodynamic responses to handgrip at 30% of maximum voluntary capacity in chagasic patients in whom parasympathetic modulation of heart rate is absent (group 1). In these patients the pressor response to isometric exercise is mediated by an increase in systemic vascular resistance. In contrast, chagasic patients with intact parasympathetic control (group 2) showed

| *During handgrip test* | | | | |
|---|---|---|---|---|
| *HR (beats/min)* | *MSAP (mm Hg)* | *CI (l/min/m$^2$)* | *SVI (ml/m$^2$)* | *SVR (dyn s cm$^{-5}$)* |
| 73 | 103 | 2 9 | 40·2 | 1845 |
| 120 | 110 | 5 0 | 41·7 | 1011 |
| 94 | 108 | 4 9 | 52 5 | 1050 |
| 94 | 122 | 5 6 | 59·6 | 1097 |
| 94 | 102 | 5 7 | 61 9 | 878 |
| 95·0 (16·7) | 109·0 (8 0)* | 4 8 (1 1) | 51 2 (10 0) | 1176 (383) |
| 76 | 84 | 3 1 | 41 3 | 1178 |
| 72 | 115 | 5·1 | 70 3 | 1049 |
| 110 | 95 | 6 3 | 57·3 | 718 |
| 96 | 102 | 5 6 | 58 4 | 819 |
| 110 | 138 | 3·7 | 32 0 | 1798 |
| 92 8 (18·1)* | 106 8 (20·9)* | 4 8 (1 3)* | 51 9 (15·2) | 1112 (424) |

haemodynamic responses that were similar to those described in normal subjects[7 26 27] in whom the pressor response is mediated by increase in cardiac output.

We found that the haemodynamic response in chagasic patients with impairment of the parasympathetic influences on the sinus node was substantially different from that seen in normal volunteers in whom the response was blocked with atropine. The normal volunteers maintained increases in cardiac output and arterial pressures.[7] Although the body position and the magnitude of isometric exercise (30% of maximum voluntary capacity) were the same in both studies, Martin *et al* measured haemodynamics in the third minute of handgrip rather than in the second minute as we did in this study. It has been suggested that the heart rate and the cardiac output may not stabilise completely when the isometric exercise is performed at higher levels of muscle tension.[1 28] Furthermore, Martin *et al* gave fixed doses of 2·0 mg of atropine to their subjects, a dose that in some individuals might have been well below the 0·04 mg/kg body weight recommended for effective blockade of the parasympathetic system.[29 30] These differences may explain why after atropine Martin *et al* found that their normal volunteers still had a substantial mean heart rate increase of 12 beats/minute and an average increase of 650 ml in cardiac output.[7] Apart from the fact that short term pharmacological blockade may not entirely reproduce the effects of chronic interruption of vagal efferents that is seen in Chagas's disease, parasympathetic withdrawal may have contributed to the chronotropic responses to handgrip seen in the subjects studied by Martin *et al.*[7] As a consequence, the pressor response still made an important contribution to the increase in cardiac output. Nevertheless, as in our group 1 of chagasic patients, the systemic vascular resistance increased in 10 of 12 normal subjects who performed handgrip after administration of atropine.[7]

Chagasic patients in group 1 undoubtedly had no parasympathetic regulation of sinus node function. Not only was heart rate reflexly unresponsive to an increase of blood pressure after the performance of the Valsalva manoeuvre, but there was also no resting vagal tonus acting upon the sinus node, as was demonstrated by the lack of chronotropic changes after atropine. Therefore, it is conceivable that parasympathetic impairment, which is the hallmark of cardiac autonomic disturbances in Chagas's disease both in anatomical[31-33] and functional terms,[19-25 34] was responsible for the abnormal cardiovascular response to isometric exercise. Whether there is concomitant impairment of sympathetic system mediated control of heart rate in chagasic patients is debatable. In some studies in which the response to passive postural stimulation was studied adrenergic control of heart rate was shown to be deficient,[22 23] but other results derived from tests that elicit higher degrees of stimulation such as dynamic exercise[21 35] militate against this possibility. The findings of the present work do not exclude impairment of the sympathetic control of the sinus node as a minor contributory factor to the abnormal haemodynamic responses to handgrip seen in group 1. Unaltered pressor responses to handgrip were seen after propranolol[7 36]; however, no change in cardiac output was seen, and the pressure rise depended upon an increase in systemic vascular resistance. On the other hand our findings confirm the normal sympathetic control of vascular tone in chagasic patients, as already shown in previous studies.[20 22 23]

Having showed that in some chagasic patients an increase of systemic vascular resistance rather than an increase in cardiac output mediates blood pressure rise during isometric exercise, it is interesting to speculate about the functional consequences of such haemodynamic alterations. Because isometric exercise is common during daily active life, these patients must face frequent afterload challenges that do not arise when chronotropic responses are normal. The situation resembles that in untreated hypertensive patients.[14 37] Our patients had neither systemic hypertension nor demonstrable clinical reduction in myocardial reserve. As the disease progresses, however, left ventricular function may become abnormal in chagasic patients. Studies in ischaemic heart disease,[26 27 38] and in other myocardial diseases,[26 27 38 39] show that although the heart rate response is impaired the pressor response to isometric exercise may even be potentiated when there is left ventricular dysfunction. Moreover, isometric exercise has been recently shown to disclose abnormal left ventricular function in chagasic patients with otherwise normal performance at rest.[40] Therefore, it seems reasonable to conclude that chagasic patients with impaired parasympathetic responses have less effective left ventricular ejection during their customary activities than do individuals who are capable of normal heart rate responses to isometric exercise. Such functional abnormalities could increase the chronic stresses imposed on left ventricular performance. No demonstrable correlation has been shown between autonomic impairment and myocardial depression in Chagas's disease, and a prospective follow up study is now underway in our laboratory to evaluate the effect of autonomic disturbances on the development of ventricular dysfunction and outcome in patients with Chagas's heart disease.

This research was partly supported by grants of the Conselho Nacional de Desenvolvimento Cientifico e Technológico.

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*Br Heart J* 1986; **55**: 211–3

# Radiation of anginal pain to the legs

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SUMMARY Pain radiated from the chest to one or both legs (17 cases), or from the legs to the chest (two cases) in 19 patients with angina or acute myocardial infarction. The leg pain was assumed to be related to the angina pectoris when both were of a similar character and occurred together, when the leg pain occurred at rest, and when there were normal peripheral pulses in the leg. Pain was felt in the left leg by 10 patients, the right leg by two patients, and in both legs by seven. Three patients experienced pain in the thigh(s), six in the shin(s), and 10 had pain in both. In six patients the pain extended down to the inner two to four toes. The pain was always felt in front of the legs. This distribution accords with the suggestion that some sensory cardiac nerve fibres occur in the lumbar sympathetic ganglia and that pain is projected into the corresponding dermatomes.

Despite improved diagnostic techniques, a history of angina is important in the diagnosis of ischaemic heart disease.[1-3] A knowledge of the variations of anginal pain, including uncommon ones, will avoid errors in the diagnosis of a common disease.

We noticed that angina can extend to the legs in some patients with ischaemic heart disease.

## Patients and methods

In 19 patients with ischaemic heart disease (16 men and three women, aged 27–73) angina was felt not only in the chest but also in one or both legs. We assumed that the pain in the legs was an extension of the cardiac pain when (*a*) it was associated with chest pain due to typical angina or acute myocardial infarction or both; (*b*) the diagnosis of angina was supported by electrocardiographic criteria at rest or during an exercise test or both; (*c*) there was pain in one or both legs which resembled the chest pain and occurred at the same time; (*d*) rest angina or acute myocardial infarction or both occurred with similar extension of the chest pain to the legs at some stage of the disease; and (*e*) normal arterial pulses were present in the legs. The last two criteria were included to exclude coincidental intermittent claudication occurring with anginal chest pain during effort.

## Results

All 19 patients had typical ischaemic chest pain. In 15 patients there was effort angina with chest pain of typical quality and distribution, and in 13 of these there were electrocardiographic changes indicating ischaemia during rest or during an exercise test or both. In eight of these patients coronary angiograms showed important coronary stenosis. The two patients with a normal resting electrocardiogram without (one case) or with doubtful (one case) exercise test both had positive coronary angiograms. All 15 patients also felt pain in one or both legs which passed off a few minutes after stopping physical effort or after taking sublingual glyceryl trinitrate or after both. Chest pain and leg pain or numbness resolved simultaneously. At some time these patients had also had chest pain at rest with radiation of pain to the legs. Seven patients had unstable angina and others had sporadic attacks of rest angina which occurred spontaneously (six cases) or during paroxysmal supraventricular tachycardia (one case) or during an attack of acute myocardial infarction (six cases).

The remaining four patients had no effort angina. One of them was a 27 year old man who had a constrictive pain across the chest, which radiated to both arms and the jaw; at the same time he had similar pain along the front of the right thigh and shin. Pain coincided with attacks of paroxysmal supraventricular tachycardia and was relieved immedi-

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Accepted for publication 3 September 1985

Table *Angiographic findings in patients with radiation of angina to the legs*

| | *No of patients* |
|---|---|
| Coronary angiography: | |
| Three vessel disease | 4 |
| Two vessel disease | 4 |
| One vessel disease (proximal LAD) | 1 |
| Aortography: | |
| Normal vessels | 8 |
| Minor stenosis in the femoral artery | 1 |

LAD, left anterior descending

ately the tachycardia ended. The second patient was a 42 year old man who had severe constrictive pain in the upper surface and three or four inner toes of the right foot, which spread up to the right inguinal area and hypogastrium, and then extended widely across the chest. The next day the pain recurred but this time it started in both feet. The electrocardiogram showed T wave inversion in the inferior leads. The next morning the electrocardiogram showed a typical Wolff-Parkinson-White pattern which has persisted and has masked the evolution of other electrocardiographic changes. Estimation of cardiac enzymes suggested an evolving acute myocardial infarction. The third patient had had two episodes of acute myocardial ischaemia at rest six years before and an acute myocardial infarction one month before admission; during all three attacks there was extension of the chest pain to the left thigh. The fourth and last patient had had an inferior wall infarction in 1982 and five attacks of typical though prolonged angina pectoris occurring at rest during the past three months. Both during acute myocardial infarction and rest angina, the pain was felt in the left shin from below the knee to the four innermost toes.

Ten of the 19 patients had coronary angiography, and in all it showed important coronary artery disease (Table).

Pain spread to the left leg in 10 patients, the right leg in two patients, and to both legs in seven cases. In all cases it affected the front of the legs. The pain affected the thigh(s) in three patients; the shins in six; both in ten, and in one patient it was more widely distributed. In two cases pain spread from the legs to the chest. In six it extended to the feet and to two to four of the inner toes.

In all 19 cases the peripheral pulses in the legs were normal. Aortography was carried out in nine patients (Table) and was normal in eight, while in one there was slight narrowing (40%) of the right deep femoral artery. The arteries of the left leg in which the pain was felt were normal.

## Discussion

The chest is the classic site of angina and such pain often extends to the upper half of the body, particularly the arms and forearms, the neck, the jaw, and the interscapular areas.[1 4 5] Its extension to the lower half of the body, particularly to the legs, is not so well recognised. Textbooks[5-7] and review articles[2 8] indicate that angina rarely if ever extends below the epigastrium. Extension of angina to the legs in two out of 160 patients was reported by McKenzie in 1923.[9] We believe that this radiation of the pain is considerably more common than the few reported cases indicate.

We report 19 cases of chest pain due to angina or acute myocardial infarction or both in which pain was also felt in the legs. The possibility that pain in the legs was caused by coexistent intermittent claudication was excluded by the presence of normal peripheral arterial pulses in the legs and the occurrence of the pain in the legs during rest angina or acute myocardial infarction.

In these patients angina spread to the thighs, the shins, or both and in some cases also extended to the feet including the inner two to four toes, but not the small toe. The pain was more common in the left leg. Both legs were affected in some cases. In general angina radiated from the chest to the legs but in two patients it spread from the legs to the chest. The pain was felt in the front of the legs whereas the pain of intermittent claudication is felt mainly in the backs of the legs. Anterior tibial compartment syndrome, which is caused by muscle oedema and tension of the fascia tibialis, produces pain resembling angina at the front and sides of the shin[10 11] and the occurrence of pain in the thigh or foot excludes this syndrome. Even when the angina is limited to the tibial area, anterior tibial compartment syndrome, which predominantly affects very young people, is highly unlikely to be found coincidentally in a patient with typical angina pectoris and such a diagnosis would certainly be excluded when there is also angina pectoris at rest, as was the case in all of our patients.

The mechanism of extension of angina to the legs could be the result of some sensory cardiac nerves being present in the lower sympathetic ganglia, rather than being restricted to the seventh and eighth cervical and the first four or five thoracic sympathetic ganglia,[4 6 12] and the consequent projection of angina to the corresponding dermatomes. The extension of the pain to the front of the legs and the four inner toes is compatible with the presence of sensory cardiac nervous fibres in the lumbar sympathetic ganglia, whereas the backs of the legs and the small toe are innervated by the sacral sympathetic ganglia.[12]

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*Br Heart J* 1986; **55:** 214–5

## *Case reports*

# Cardiac tamponade in a case of meningococcal meningitis

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SUMMARY A 17 year old girl developed cardiac tamponade during the course of a meningococcal meningeal illness. Pericardiotomy was eventually required to alleviate the tamponade.

### Case report

The patient, a 17 year old girl, presented to another institution with a 36 hour history of headache and vomiting. On admission she was pyrexial and had pronounced photophobia and neck stiffness. Cardiac auscultation was normal. The clinical diagnosis of meningitis was confirmed when a lumbar puncture yielded cloudy cerebrospinal fluid containing no glucose, protein >200 mg/dl, white cell count >12 000 cells/ml. Staining showed gram negative intracellular diplococci, and culture confirmed the growth of *Neisseria meningitidis*.

Treatment with intravenous benzyl penicillin, one megaunit hourly, was started. The next day she became tachypnoeic and later complained of pleuritic chest pain. Auscultation showed a pleuropericardial rub. Electrocardiogram showed changes consistent with pericarditis. Echocardiography one day later showed a moderately large pericardial effusion without evidence of tamponade. White cell count was 14 300 × $10^9$/l of which 90% were polymorphs. She was transferred to our unit for specialist care.

Forty eight hours after transfer her condition deteriorated and pronounced respiratory distress developed. Echocardiography showed enlargement of the pericardial effusion with tamponade, as demonstrated by right ventricular outflow tract collapse during diastole.

Pericardiocentesis produced 200 ml of turbid straw coloured fluid, containing abundant white cells, 50% of which were polymorphs and 50% lymphocytes. The fluid contained 100 mg/dl of protein. Gram stain and culture were negative. The patient improved considerably but only transiently. Thirty six hours later echocardiography again showed tamponade, but on this occasion a large solid element could be seen impinging on the right ventricle (Figure). This was presumed to be thrombus secondary to aspiration trauma. The patient's condition deteriorated and white cell count was 23 000 × $10^9$/l.

A further pericardiocentesis was attempted, but it was impossible to aspirate sufficient fluid to alleviate the tamponade. In consultation with the cardiac surgeon pericardiotomy was deemed to be necessary.

At operation several very large fibrin clots were noted, compressing the right and left ventricles. More than 400 ml of sterile cloudy fluid was removed from a very fibrinous pericardial sac. The volume of the fibrin clots was estimated to be >100 ml.

Postoperative recovery was uneventful and the patient was discharged two weeks later. There was no further complication at a follow up at four months.

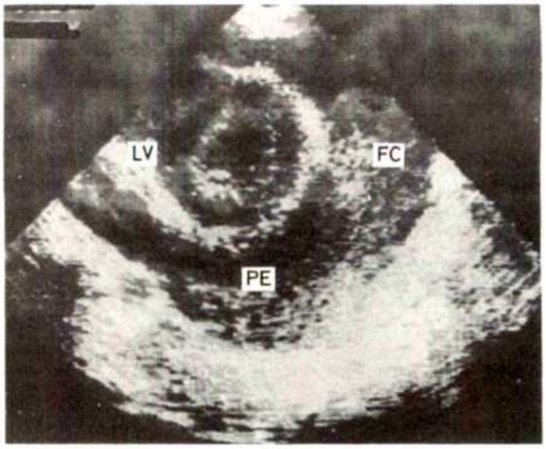

Figure *Echocardiograph in parasternal short axis view showing large fibrin clot in pericardial effusion. LV, left ventricle; PE, pericardial effusion; FC, fibrin clot.*

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## Discussion

Pericarditis complicating meningococcal infection has been well described. The reported incidence varies from $<1\%$,[1 2] to 4–6%,[3] to as much as 19%,[4 5] depending on the various criteria used. Cardiac tamponade as a complication of primary meningococcal pericardial infection is also well described, but review of published reports showed only five cases of tamponade caused by primary meningeal infection.[3 4 6 7]

The effusion is commonly believed to be secondary to bacterial seeding of the pericardium. Herrick in 1918 who described 12 cases of pericarditis secondary to meningococcal meningitis found at least two cases with positive gram stain in the pericardial aspirate; indeed one of these cases had tamponade as well.[3] Morse *et al*, however, believe that the effusion is likely to be secondary to an immunological hypersensitivity reaction.[4]

In our case, in view of the rapid onset of the effusion, the large number of white cells in the aspirate, and the fibrinous nature of the effusion and pericardium, we feel that bacterial seeding is likely to be the cause of the effusion.

Of the five previously described cases, one was not diagnosed until after death,[3] the others were all treated by pericardiocentesis, and two cases were also given steroids.[6 7] The presence of fibrin clots and the failure of pericardiocentesis in our case led us to surgery. We believe this to be the first reported case of tamponade secondary to meningeal meningococcal infection that has required pericardiotomy.

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*Br Heart J* 1986; 55: 216–8

# Late pericardial tamponade and coronary arteriovenous fistula after trauma

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SUMMARY A 48 year old man presented with cardiac tamponade six weeks after an apparently minor penetrating chest injury. Thoracotomy showed a haemopericardium with no actively bleeding vessel. Re-investigation eleven months later, prompted by persistent chest pain, showed the presence of a fistula between the second diagonal of the left anterior descending coronary artery and a cardiac vein.

## Case report

A 48 year old man presented to another hospital having collapsed at home. He had been experiencing infrequent episodes of central and left sided anterior chest pain at rest for two years. In the week before admission the pain increased in frequency and severity and this culminated in a prolonged episode associated with loss of consciousness. There was no history of hypertension or serious illness. When he was first examined he was semiconscious, pale, and cyanosed (pulse of 120 beats per minute, blood pressure of 80/50 mm Hg). Venous pressure was raised and a fourth heart sound was heard. He was transferred to our hospital with a clinical diagnosis of possible aortic dissection and his clinical condition was unchanged on arrival at Harefield Hospital. The central venous pressure was 19 cm of water above the mid-axillary line and all peripheral arterial pulses were present and of equal strength. He had a small puncture mark on the anterior surface of the chest in the fifth intercostal space 2 cm medial to the mid-clavicular line.

An electrocardiogram showed sinus rhythm with flattening of the anterior T wave. A chest radiograph showed moderate cardiomegaly and a small left pleural effusion. A cross sectional echocardiogram showed a pericardial effusion with no features to suggest cardiac tamponade, but cardiac catheterisation showed cardiac tamponade. The right and left ventricular minimum diastolic pressures were 10 mm Hg with an end diastolic pressure of 18 mm Hg and had a characteristic dip and plateau pattern. Pulmonary and aortic angiography excluded major embolism and dissection. Coronary angiograms were not obtained at this examination.

Pure blood was obtained by pericardial aspiration and at left thoracotomy a small haematoma on the anterior surface of the left ventricle and haemopericardium were noted with no evidence of active bleeding. No other abnormality was found. An operation was performed to produce a pericardial window.

After operation he gave a clear history of a penetrating chest injury. Six weeks before admission while he was using a circular saw to cut floor boards he fractured a steel nail and a 3 cm fragment penetrated his chest. He removed the fragment and suffered some sharp chest pain but was soon able to continue working.

At follow up he continued to have episodic left sided chest pains at rest. The only new finding on examination was a quiet apical ejection murmur. Cardiac catheterisation excluded recurrent tamponade and constriction, but left ventricular angiography showed mild apical hypokinesia.

Selective coronary arteriograms showed two fistulous connections, one between the second diagonal branch of the left anterior descending coronary artery and a branch of the great cardiac vein (Fig. 1) and a second filling a small vessel within the lung (Fig. 2). Exercise testing and thallium scanning excluded cardiac ischaemia but did identify a small resting anterolateral perfusion defect.

## Discussion

This case illustrates the combination of two rare

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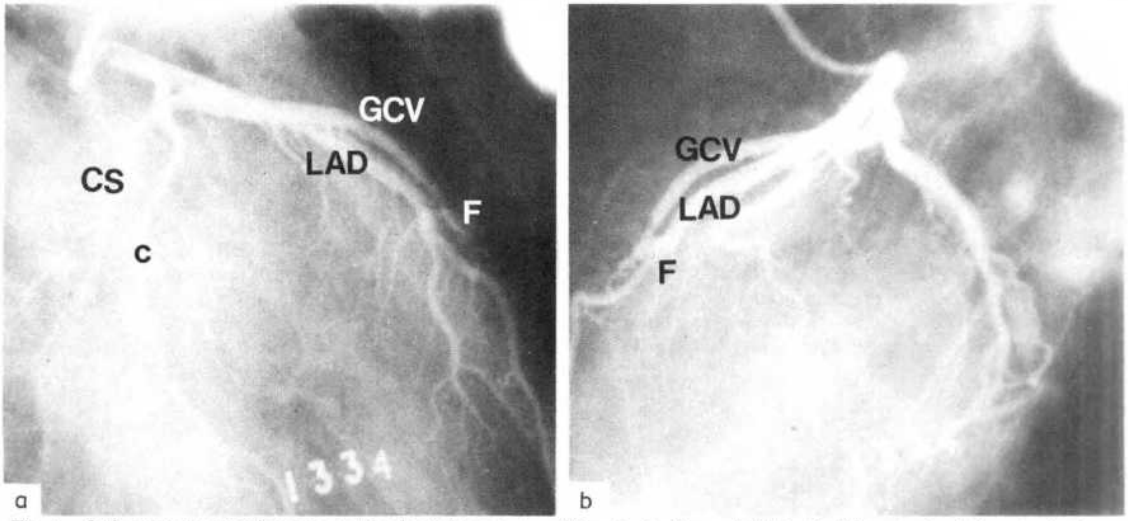

Fig. 1 *Left coronary arteriograms (a) in the right anterior oblique projection and (b) in the left anterior oblique projection. The fistula (F) can be seen arising from the second diagonal branch of the left anterior descending coronary artery (LAD) with early opacification of the great cardiac vein (GCV) and coronary sinus (CS). C, circumflex branch.*

complications of penetrating injury of the chest. Pericardial tamponade is a relatively common feature of such injuries but usually presents very early after trauma.[1 2] Delayed tamponade is much less frequent and has usually been described after surgery[3 4] and rarely after trauma.[5] The latent period of six weeks before the onset of tamponade is longer than previously described after trauma but similar to that found after operation (usually as part of the postpericardiotomy syndrome). The second feature in this case is the development of a coronary arteriovenous fistula. Fistula formation is rare after trauma and generally affects a coronary vessel and right ventricle or right atrium.[6] We found only two published reports of coronary arteriovenous fistulas.[7 8] Since selective coronary angiography was not performed before the exploration of the pericardium it is not possible to define the precise relation between the development of the fistula and intrapericardial bleeding. The development of a coronary artery to intrapulmonary fistula may follow the removal of pericardium in the region of the anterior descending artery, but in this case the fistula is more likely be related to the original injury, in view of the haematoma observed at thoracotomy.

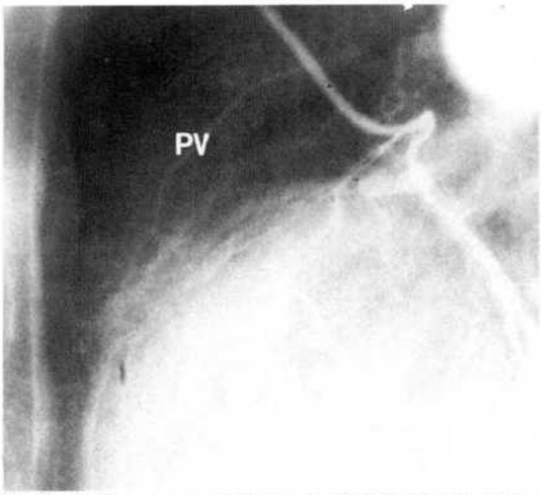

Fig. 2 *Left coronary arteriogram in the left anterior oblique projection showing filling of a pulmonary vessel (PV).*

It has been suggested that coronary arteriovenous fistulas should be closed surgically.[6] In our case the degree of shunting is small, the chest pain is not typically cardiac, and there is no objective evidence of exercise induced ischaemia. A coronary steal could theoretically arise, but this appeared unlikely because of the degree of shunting observed angiographically. Consequently the fistula has not been closed at this stage; there has been no evidence of further cardiac complications or bleeding during 15 months of follow up.

We thank Mr Alun Rees for performing the thoracotomy and for allowing us to report on this patient.

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*Br Heart J* 1986; **55:** 219–20

## *Correspondence*

# Improvement in angina pectoris with alpha adrenoceptor blockade

Sir,
Collins and Sheridan (1985; **53:** 488–92) reported that compared with placebo treatment the alpha blocker indoramin (given three times a day) improved exercise tolerance and increased oxygen consumption during exercise in patients with stable angina pectoris. These results are different from those reported by us.[1] We studied patients with stable angina pectoris who were not taking any other antianginal drugs. In a randomised crossover study we compared the effects of single doses of 50 and 75 mg indoramin with those of placebo. Exercise time to the onset of angina in seconds before and after placebo and before and after 50 and 75 mg of indoramin are shown in the table (mean (SEM)):

| | *Placebo* | *Indoramin (50 mg)* | *Indoramin (75 mg)* |
|---|---|---|---|
| Control | 279 (53) | 233 (43) | 267 (52) |
| 1 h post | 283 (49) | 313 (56) | 347 (55) |
| 4 h post | 347 (67) | 302 (47) | 341 (55) |

Thus, in contrast to the results obtained by Collins and Sheridan, we could not demonstrate any improvement in exercise performance at either of the doses of indoramin.

It is possible that the results obtained by Collins and Sheridan are different from ours because their patients were taking other antianginal agents—such as vasodilators—as well as beta blockers. Also we studied patients after single oral doses whereas Collins and Sheridan gave indoramin three times a day.

Therefore, in view of these two different reports I feel that the effect of indoramin as a single agent should be evaluated during sustained treatment in patients with exertional angina.

Udho Thadani,
Cardiovascular Section,
Department of Medicine,
University of Oklahoma,
Oklahoma City,
Oklahoma 73190,
USA.

**Reference**

1 Thadani U, Parker JO. Evaluation of alpha blocker—indoramin in angina [Abstract]. *Clin Pharmacol Ther* 1983; **33:** 211.

This letter was shown to the authors, who reply as follows:

Sir,
We have difficulty in accepting that the failure of Thadani and Parker to find an improvement in exercise performance with indoramin (based on the results presented in their comments to this journal and in the abstract cited[1]), necessarily represents the demonstration of a different response to that reported by ourselves (1985; **53:** 488–92). This is because there are serious problems in the design of their study that could readily mask an improvement in response to the drug. For example there appears to have been an appreciable training effect (as indicated by the data obtained in their placebo group) and each subject received only one dose of indoramin, which, given its high first pass clearance,[2] is unsuitable for this type of study. We believe that with such difficulties a study based on nine patients is almost certainly inadequate. Furthermore, the exercise durations they observed at one hour after treatment appear to have increased approximately 30% after active treatment, compared with 1% after placebo treatment, based on the means presented. For these reasons, we believe that an interpretation of their results as indicating a negative response to the drug could well be misleading.

In our paper we emphasised the importance of interpreting our results only in relation to patients already receiving beta blockade or nitrates and we agree that a careful study of a single agent with alpha adrenoceptor blockade in patients with chronic stable angina would be of interest.

Peter Collins,
Desmond Sheridan,
Department of Cardiology,
St Mary's Hospital,
Praed Street,
London W2 1NY.

**References**

1 Thadani U, Parker JO. Evaluation of alpha blocker-indoramin in angina [Abstract]. *Clin Pharmacol Ther* 1983; 33; 211.

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The Annual General Meeting for 1986 will take place in York on 2 and 3 April 1986, and the closing date for receipt of abstracts was 2 January 1986.

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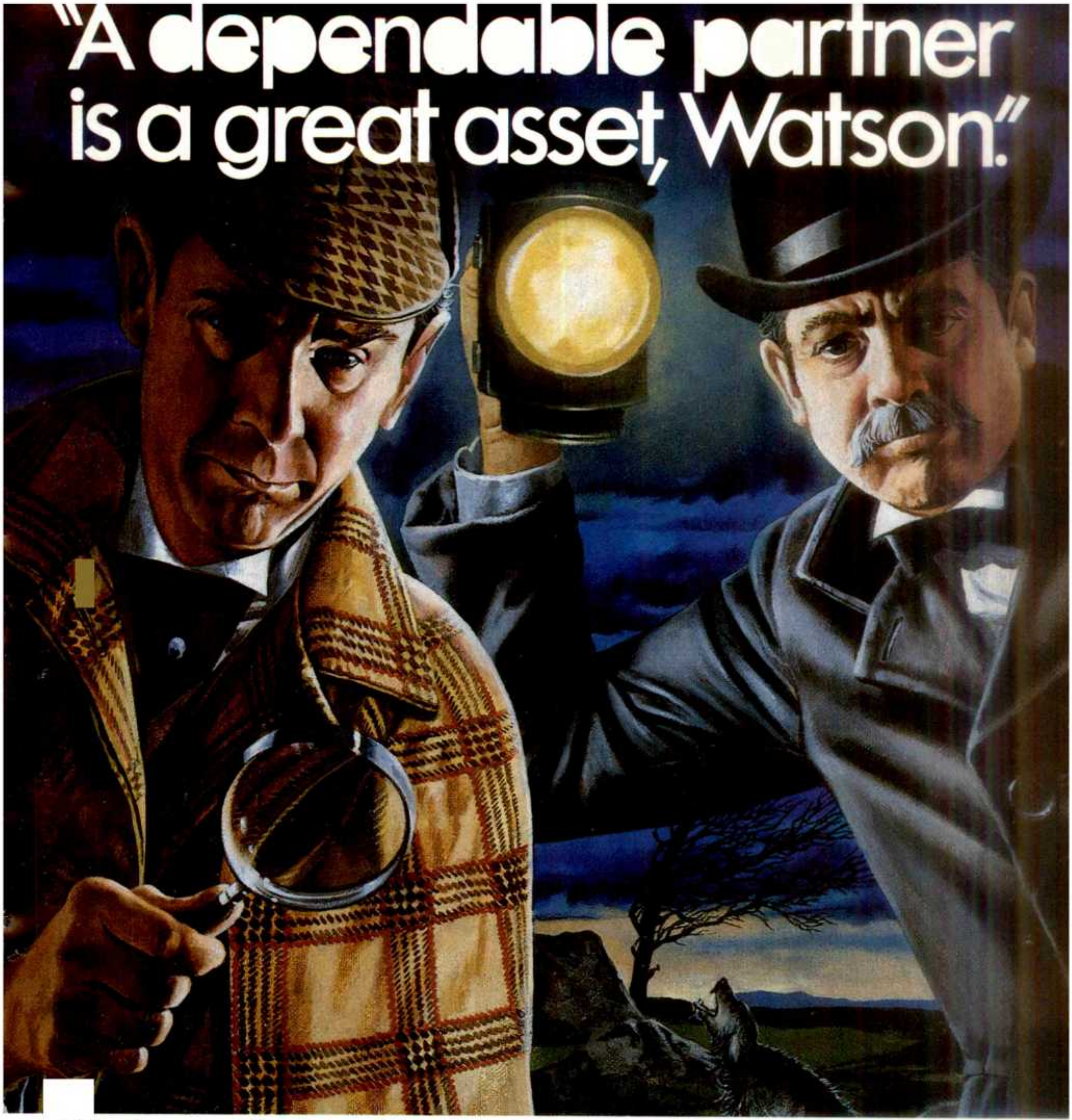
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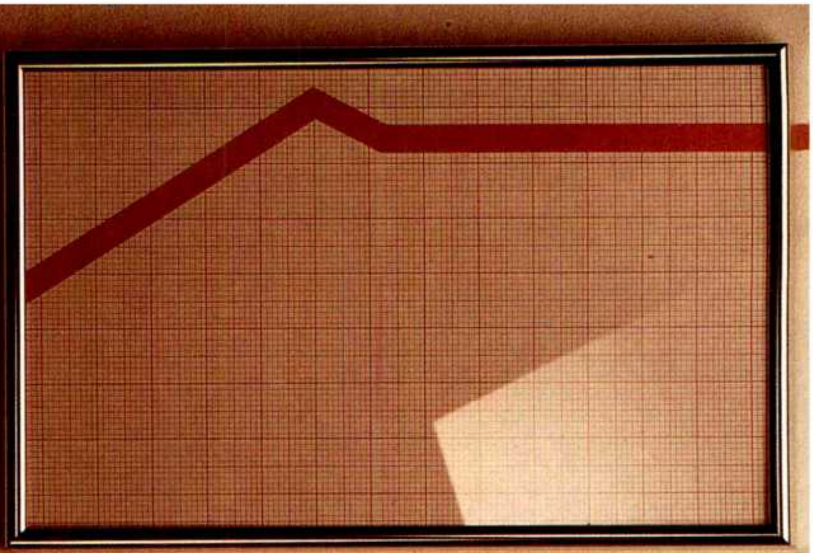

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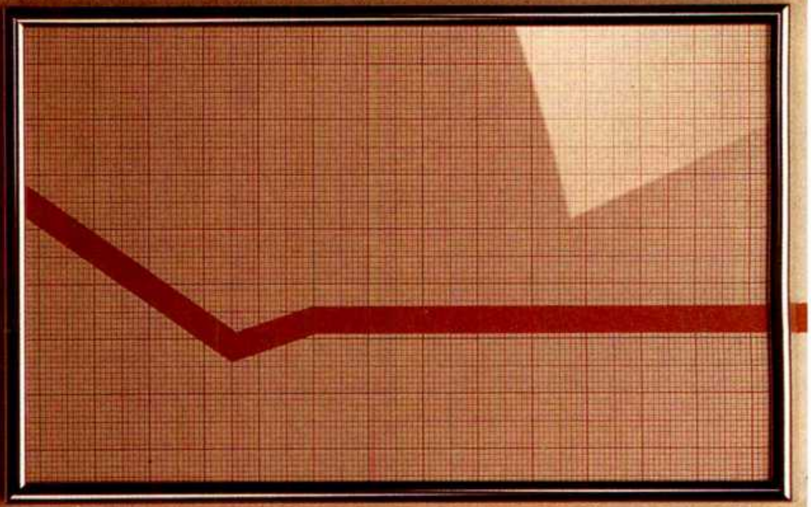

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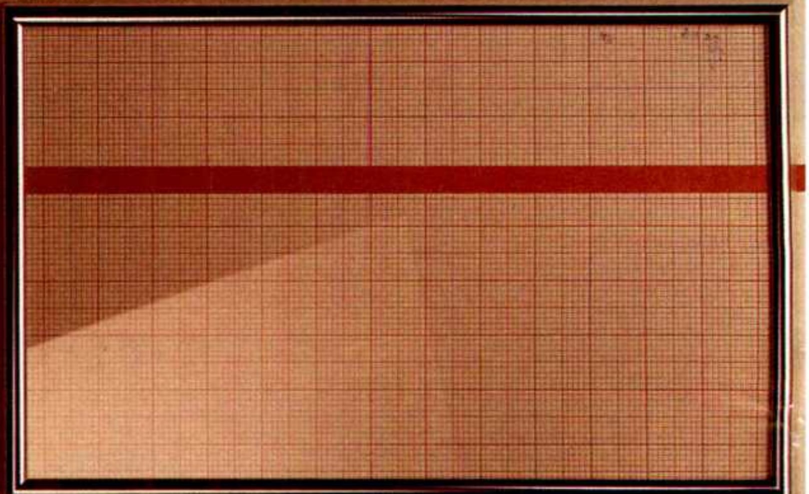

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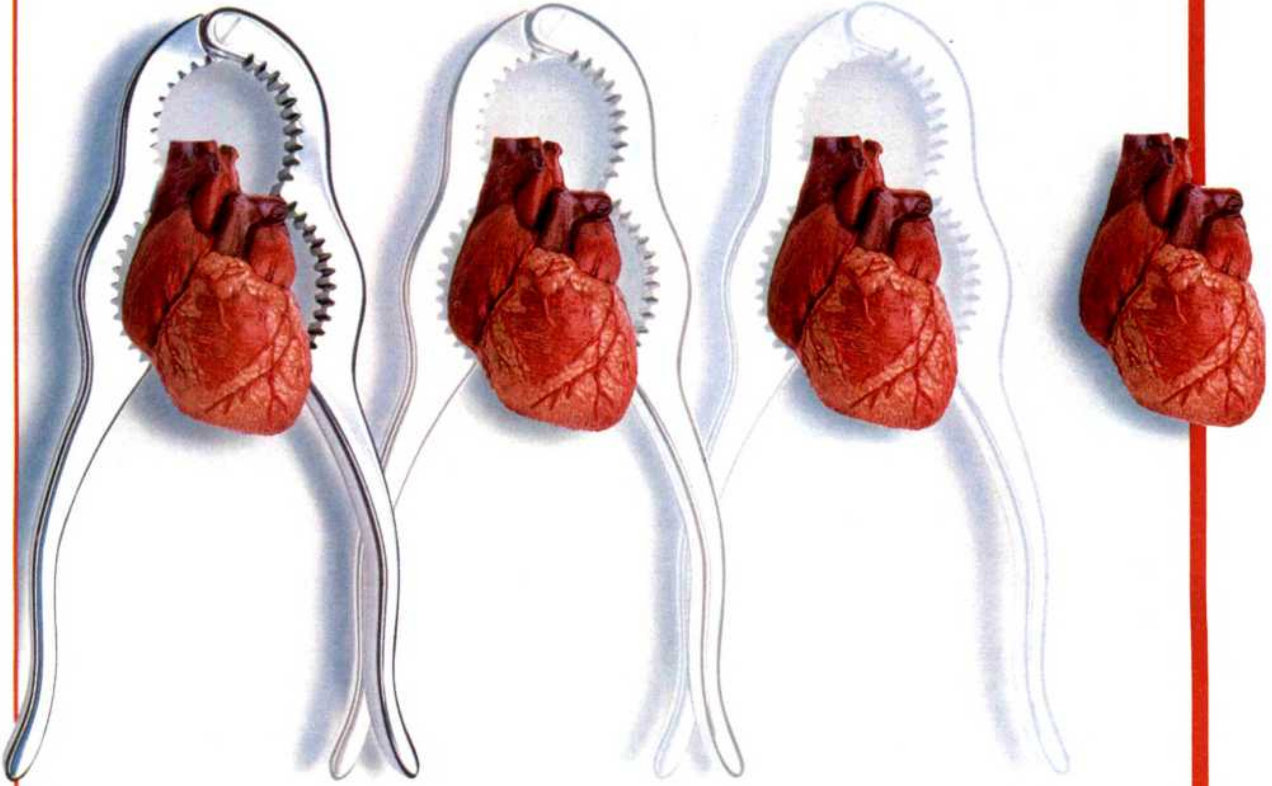

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*Br Heart J* 1986; 55: 221–2

# *Editorial*

## Coronary angioplasty—what can we reasonably expect?

G D G OAKLEY

*From the Department of Cardiology, Northern General Hospital, Sheffield*

Coronary angioplasty has proved to be an effective alternative to coronary surgery for the treatment of angina in selected patients. Many of the first patients to receive this treatment in the United Kingdom six years ago remain symptom free. Coronary angioplasty was established as a new and valuable method of treatment by the pioneering work of Dr Andreas Gruentzig. His death in a flying accident has robbed angioplasty of its acknowledged leader.

As with many new methods of treatment, coronary angioplasty was initially greeted with scepticism and was then embraced with great enthusiasm. The indications were expanded from single vessel to multiple vessel disease; from one proximal lesion to more than one lesion per vessel; from patients with recent onset of stable symptoms to those with unstable angina and those with longer histories; and from concentric stenoses to eccentric lesions, calcified lesions, and occlusions. These advances have been the result of increased operator skill and experience and of technical improvements in the equipment. Some workers have felt capable of tackling up to eight stenoses with apparently successful results.[1]

Amid all this excitement two recent papers have drawn attention to the complications of this procedure. Shiu *et al* reported an occlusion rate of 8% in 240 procedures from three centres.[2] A high proportion of these patients were women. Attempts to redilate were often successful (six out of ten attempts) and redilatation was a safe procedure if the steerable wire had been left in place across the lesion. Because this process does not take too long, it can be tried in an emergency while preparations for cardiac surgery are under way. On page 223 Norell *et al* report their early experience at the London Chest Hospital in 69 patients.[3] These workers must be congratulated on the speed and efficiency with which emergency surgery was started after failure of angioplasty. All but one of their complicated cases survived with symptomatic improvement and only one third of those patients with occlusions subsequently had an infarct. An overall failure rate of 27% with an occlusion rate of 19%, however, must have been disappointing and Norell and coworkers speculate on the reasons for this.

Coronary angioplasty is a technically demanding procedure in which there is a thin line between success and failure. The figures in the National Heart, Lung and Blood Institute register clearly show that at all centres there is a learning curve during which procedure-related complications and failure to dilate the lesion decrease.[4] The London Chest group included "three individuals who were becoming experienced" and the total number of procedures (69) was not great, so in this series none of the operators was likely to have a large experience of angioplasty. It is not clear whether these procedures were undertaken before or after recent improvements in equipment. The use of smaller soft tip guiding catheters (with and without side holes), finer steerable guide wires which permit better visualisation of the artery, and low profile balloons might have reduced the complications—particularly that of trauma to the left main stem coronary artery.

What then can reasonably be expected from a centre during the first few years of coronary angioplasty? In Sheffield 240 dilatations have been performed in 209 patients. Most of these were done by one operator who now has personal experience of over 300 cases. Technical success was achieved in 205 (85%), in 14 (6%) urgent surgery was required, and two patients died (one after discharge). There were nine (4%) Q wave infarcts (four after surgery)

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Recent occlusions, occurring between initial angiography and angioplasty, were successfully dilated in 10 out of 17 attempts. Unstable angina accounted for 20% of the cases and two-vessel dilatations were performed in only 12 patients. These results are similar to those from other centres and have improved gradually. They reflect increasing experience, and the use of more appropriate equipment and patient selection. We have found that less than 10% of patients considered for revascularisation are suitable for angioplasty, and that it is unusual to find multivessel disease in which all important lesions are amenable to dilatation.

Technical success is not always followed by prolonged symptomatic relief. Late recurrence of symptoms (that is, after six months) is usually due to progression of disease, but early recurrence is due to restenosis of the angioplasty site. Angiographic restenosis may occur in up to 30% of patients. Symptomatic restenosis occurs in 10–15% of patients but in this group repeat angioplasty is safer, easier, and more successful than the initial procedure. Not much is known about the factors governing restenosis—it occurs later than one day and earlier than three months. Restenosis is not clearly related to any technical factors at the time of angioplasty, nor to any particular patient features. It will be interesting to see the results of attempts to improve the radiographic appearance of the dilatation and to reduce platelet aggregation at the angioplasty site with epoprostenol (prostacyclin).

The role of angioplasty continues to expand. It has a definite place in the treatment of unstable angina.[5] It will almost certainly be valuable in acute myocardial infarction after the use of selective thrombolytic agents. The value of angioplasty in complex multivessel disease is unclear because so far there has been no long term follow up. No comparative trial of angioplasty versus surgery and medical treatment has so far been performed because of the difficulties inherent in such a study. A trial is planned in the United States and this will include patients with multivessel disease.

Coronary angioplasty and bypass graft surgery are complementary procedures. One clear message from the paper by Norell *et al* is that we are still a long way from being able to dispense with surgical back up to prevent or reduce the extent of infarction after complicated angioplasty. Coronary graft stenoses, on the other hand, may also be amenable to dilatation. Angioplasty also preserves the saphenous veins for future operation if the disease progresses. It is unlikely that coronary angioplasty will reduce the demand for bypass surgery. Referrals for angiography, especially in younger patients with short histories, will increase. Only some of them will be suitable for dilatation and the rest will join the ever increasing queue for bypass grafting.

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*Br Heart J* 1986; 55: 223–6

# Outcome of early surgery after coronary angioplasty

MICHAEL S NORELL, JOHN LYONS, CLIVE LAYTON, RAPHAEL BALCON

*From the Cardiac Department, London Chest Hospital, London*

SUMMARY Nineteen of 69 patients undergoing coronary angioplasty required immediate coronary surgery after the procedure. Six of these operations were planned as a result of angioplasty that failed without producing any complication. The remaining 13 cases were operated upon because complications occurred during angioplasty. These were coronary artery dissection in four, occlusion in five, continuing severe spasm in two, tamponade in one, and in one other detachment of a guidewire tip. In these 13 cases the vessel in which angioplasty had been attempted was the left anterior descending coronary artery in eight, the right in four, and the circumflex artery in one. This distribution was no different from that in the 56 patients without complications.

There was one early postoperative death due to extensive anterior myocardial infarction, and there was electrocardiographic evidence of new infarction in three other patients. A mean of 16 months postoperatively, 16 of the 18 surviving patients had no cardiac symptoms, while angina had improved in the remaining two. Sixteen of the 18 patients had nuclear left ventricular angiography after a mean of 27 months. When the results of this investigation were compared with the left ventricular cineangiograms performed before angioplasty was attempted only two patients showed evidence of a new left ventricular wall motion abnormality.

Prompt operation after complications of angioplasty is usually successful with good symptomatic relief and without left ventricular damage. The incidence of complications requiring operation, however, was high in this group of patients, most of whom had single vessel coronary artery disease.

Coronary angioplasty is increasingly used in selected patients with coronary artery disease. Complications occurring during the procedure, however, result in the need for emergency surgery in approximately 6% of cases.[1] This paper reviews our experience of the immediate and long term outcome of urgent surgery after angioplasty.

## Patients and methods

All patients undergoing coronary angioplasty had at least moderately severe angina despite full medical treatment, and they were therefore selected to have surgery if angioplasty was not successful.

Left ventricular cineangiography was performed in the 30° right anterior oblique projection, and normal left ventricular wall motion was demonstrated in all but four patients. The ejection fraction was measured by planimetry of the end systolic and end diastolic frames (mean ejection fraction 58%, range 20–72%).

Before angioplasty was attempted, all patients were given premedication with oral nitrates, nifedipine, and dipyridamole. In all cases a surgical team was aware that an angioplasty was being undertaken. The procedure was scheduled such that in the event of a complication occurring one of two operating theatres would be available for emergency surgery.

### FOLLOW UP

The frequency of myocardial infarction after surgery was determined on the basis of the following electrocardiographic criteria: new Q waves, loss of R wave, and new bundle branch block. The average duration of follow up was 16 months (range 1–45

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Accepted for publication 8 October 1985

months) at which time any cardiac symptoms were noted.

Nuclear left ventricular angiograms were obtained a mean of 27 months after surgery (range 2–54 months). A dose of 0·03 ml/kg body weight of Amerscan stannous agent was injected intravenously. After 30 minutes 20 mCi of 99m-technetium pertechnetate was injected into an arm vein. After a further five minutes the patient was scanned while supine in a 45° left anterior oblique position with a large field Siemens gamma camera. The patients performed symptom limited bicycle exercise in a supine position. Gated acquisition took place during the three minutes of the final stage reached.

Left ventricular wall motion analysis was reported by an independent observer who was unaware of the patients' clinical details. We used Student's paired *t* test for statistical analysis.

## Results

Nineteen (27%) of the 69 consecutive patients undergoing angioplasty required urgent coronary artery surgery (Table). There were 11 men and eight women with a mean age of 55 years (range 47–73 years). All had at least moderately severe angina despite appropriate medical treatment, with 11 having had at least one previous episode of angina at rest. No patient had sustained a recent myocardial infarction and in all cases the angioplasty was performed electively. Fifteen patients had single vessel coronary artery disease defined as a lesion producing at least 70% luminal narrowing in one major coronary artery. This affected the left anterior descending artery in 11, the right in three, and the circumflex coronary artery in one patient. Four patients had two vessel disease. All of them had right coronary artery disease, three with additional left anterior descending artery disease and one with circumflex artery disease. In three of these four patients angioplasty of only one vessel was attempted, while in one a double procedure was attempted.

### INDICATIONS FOR SURGERY

In six patients the stenosis could not be crossed with the dilatating balloon catheter, no complication occurred, and they proceeded to surgery. In nine others in whom the lesion could not be crossed and the remaining four in whom the stenosis had been crossed a complication necessitated urgent surgery.

Table *Patients who required early coronary artery surgery after angioplasty*

| *Case No* | *Age* | *Sex* | *Angina grade* | *Stenosis site* | *LV EF %* | *Wall motion abnormality* | *Complication* | *Time to bypass (min)* | *Grafts applied* | *Postoperative data* | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | *ECG* | *Angina grade* | *LVEF% (exercise)* | *Wall motion abnormality* |
| 1 | 56 | F | 3 | LAD | 68 | Apical | — | — | LAD | — | 0 | 53 | Apical |
| 2 | 57 | M | 4 | RCA | 70 | — | — | — | RCA | — | 0 | 58 (67) | — |
| 3 | 62 | F | 3 | LAD,* RCA | 51 | Anterior | — | — | LAD, RCA | — | 0 | 37 (30) | Anterior |
| 4 | 54 | M | 4 | LAD | 39 | Apical | — | — | LAD | — | 0 | 35 (39) | Apical |
| 5 | 57 | F | 3 | LAD | 50 | — | — | — | LAD | — | 0 | 45 (55) | — |
| 6 | 71 | F | 4 | LAD, RCA* | 57 | — | — | — | LAD, RCA | — | 0 | Unavailable | |
| 7 | 66 | M | 4 | LAD | 60 | — | LAD occlusion | — | LAD diagonal | Anterior Q waves | 0 | 31 | Anterior |
| 8 | 73 | F | 3 | LAD | 69 | — | LCx dissected | 180 | LAD, LCx | Bundle branch block | 0 | 58 (67) | — |
| 9 | 56 | M | 4 | RCA,* LCx | 20 | Anterior | RCA dissected | 150 | RCA, LCx | — | 0 | 39 (43) | Anterior |
| 10 | 47 | M | 4 | LAD | 71 | — | LMS perforated | 95 | LAD, LCx | — | 0 | 61 (68) | — |
| 11 | 56 | M | 3 | LAD | 47 | — | LAD occluded | — | LAD, LCx | — | 1 | 54 | — |
| 12 | 54 | M | 4 | LAD | 49 | — | LAD spasm | — | LAD | — | 2 | 62 (59) | — |
| 13 | 62 | M | 4 | LAD | 55 | — | LAD occluded | 240 | LAD, RCA | — | 0 | 48 (58) | — |
| 14 | 49 | M | 3 | LCx | 60 | — | LMS dissected | 60 | LAD, LCx | Anterior Q waves | | Died | |
| 15 | 50 | M | 3 | LAD | 70 | — | LAD occluded | 88 | LAD | — | 0 | 60 (61) | — |
| 16 | 54 | F | 4 | LAD,* RCA* | 71 | — | RCA dissected | 60 | LAD, RCA | Reduced inferior R wave | 0 | 28 (24) | Apical |
| 17 | 55 | F | 4 | RCA | 72 | — | RCA occluded | 150 | LAD, RCA | — | 0 | 56 | — |
| 18 | 54 | M | 3 | RCA | 61 | — | RCA spasm | 60 | RCA | — | 0 | Unavailable | |
| 19 | 60 | F | 4 | LAD | 71 | — | Guidewire tip detached | 60 | LAD diagonal LCx | — | 0 | 58 (45) | — |

*Vessel attempted.

LAD, left anterior descending, RCA, right coronary artery, LCx, left circumflex; LMS, left main stem, LVEF, left ventricular ejection fraction

### COMPLICATIONS OF ANGIOPLASTY

Coronary artery dissection occurred in four patients. The right coronary artery was dissected in two and a lateral circumflex in another. These patients developed severe chest pain and ST segment elevation. The left main stem was dissected in another patient who developed a profound bradycardia and became hypotensive.

The coronary artery became occluded without apparent dissection in five patients (in four in an attempt to dilatate a left anterior descending artery lesion and in one a right coronary artery lesion). All five developed severe pain and ST segment elevation and therefore went on to surgery. In two patients coronary artery spasm was assumed to have occurred after initially successful dilatation of a left anterior descending lesion in one and of a right coronary stenosis in another patient. In both cases there had been transient occlusion after dilatation which had temporarily reopened after intracoronary nitrates. The subsequent occlusion had been persistent, and surgery was undertaken because of pain and ST segment elevation.

One patient developed pericardial tamponade. He had become markedly hypotensive after an unsuccessful attempt to cross a stenosis of the left anterior descending coronary artery and at emergency surgery it was apparent that the left main stem had been perforated. In another patient with a stenosis of the left anterior descending artery the fixed guidewire tip of the balloon catheter became detached and lodged in the main circumflex artery. Though there was no clinical deterioration, it was felt that surgery should be performed.

In the 13 cases with complications of angioplasty the stenosis that we attempted to cross was in the left anterior descending artery in eight (62%), the right coronary artery in four (31%), and the circumflex artery in one (7%). This frequency resembled that in 56 patients who had undergone attempted angioplasty without the occurrence of a complication.

While emergency surgery was being arranged the patients received intravenous nitrates, sublingual nifedipine, and diamorphine. Intra-aortic counterpulsation balloon pumps were not inserted. One patient (case 16) developed ventricular fibrillation requiring direct current defibrillation and another (case 14) required external cardiac massage until cardiopulmonary bypass was established.

### SURGERY

The interval (mean 114, range 60–240 minutes) from the recognition of a complication at angioplasty to the patient being put on cardiopulmonary bypass was known in 10 of the 13 complicated cases.

Seven of the 15 patients with single vessel disease received a single vein graft. Seven of the other eight patients with single vessel disease had two vein grafts. In three this was for mild disease in another vessel while in one the lesion was proximal to a diagonal vessel which was therefore also grafted. The remaining three patients with single vessel disease received additional grafts as a direct result of the angioplasty. In one a lateral circumflex artery had been dissected during attempt to dilatate a lesion of the left anterior descending artery. Two patients had sustained damage to the left main stem and both required left anterior descending and circumflex grafting.

One patient (case 19) with stenosis of the left anterior descending artery required three vein grafts. In this case the fixed guidewire tip of the balloon catheter had become detached and lodged in the main circumflex artery. This vessel was explored in an unsuccessful attempt to recover the guidewire tip, and was therefore also grafted in addition to the left anterior descending and diagonal arteries which had been grafted because of a proximal lesion in the left anterior descending artery.

### MYOCARDIAL INFARCTION

There was evidence of new infarction in four patients. One of these (case 14), in whom the left main stem had been dissected, developed an extensive anterior myocardial infarction and was moribund before an emergency operation was performed. He did not survive. The other three patients were also from the group with complications and one of them had occluded left anterior descending artery. The other two had dissection of right and circumflex arteries.

### SYMPTOMS

Sixteen of the 18 surviving patients had no cardiac symptoms at follow up. Angina had improved in the remaining two.

### LEFT VENTRICULAR FUNCTION

Nuclear left ventricular angiography was not performed on two patients. One had an occlusion of the right coronary artery during angioplasty without evidence of infarction, had proceeded to successful operation, and was subsequently symptom free. The other had had no complication at angioplasty and was also symptom free after operation.

In the remaining 16 patients analysis of ejection fraction showed a small but significant reduction in mean ejection fraction at rest (58% *vs* 49%, $p<0.05$). Ejection fraction rose on exercise in five of the eight patients studied.

Analysis of left ventricular wall motion in 16 patients showed that only two had developed new segmental abnormalities. Both had had normal left ventricular contraction on their left ventricular cineangiograms before angioplasty but had new anteroapical wall motion abnormalities in the follow up nuclear angiogram. Both had sustained an occlusion of the left anterior descending artery during attempted angioplasty.

## Discussion

The place of urgent coronary artery surgery after complicated angioplasty is unclear. Our experience shows that it is feasible and the frequency of myocardial infarction (31%), as judged by electrocardiographic changes, suggests that this is not an inevitable sequel of complicated angioplasty. These data resemble those of the National Heart, Lung and Blood Institute Registry.[1] This reported that 26% of patients requiring urgent surgery developed Q wave infarction (52 of 202 patients) and similar results have been reported by others.[2]

There is evidence that prompt revascularisation within two to three hours of the onset of myocardial ischaemia may limit the extent of infarction.[3] This resembles the circumstances in the patients with complications, most of whom were on cardiopulmonary bypass within two hours. Other factors which may have contributed to the relatively low frequency of infarction despite coronary artery occlusion, are the presence of collateral flow distal to the damaged artery and the possibility of spontaneous thrombolysis. The reversal of previously persistent coronary artery spasm may have been another factor, as may premedication with calcium antagonists which could have protected a potentially ischaemic myocardium[4].

The frequency of complications requiring urgent coronary artery surgery during angioplasty in this group is high compared with that reported in other series in which emergency surgery was required by about 6% of patients.[1] Our patients were operated on by three individuals who were becoming experienced in angiography and this in part accounts for the high complication rate. Complications such as those described here are often treated by repeat angioplasty rather than by surgery.[5 6] Since, however, the duration of myocardial viability is dependent on unknown variables such as the extent of collateral flow, at the time of this study we took the view that once obstruction had occurred it was unlikely that revascularisation could be achieved soon enough by attempting repeat angioplasty. This approach accounts for the high rate of emergency surgery. Subsequent experience, however, has demonstrated that our view was not correct.

Despite the relatively good results of surgery in terms of symptoms and left ventricular function in these patients, morbidity and mortality were high in a group in which most patients had only single vessel disease and normal left ventricular function. Our experience emphasises that operators acquiring experience of the technique should only select for angioplasty those patients whose angina on medical treatment is important enough to make them candidates for surgery.

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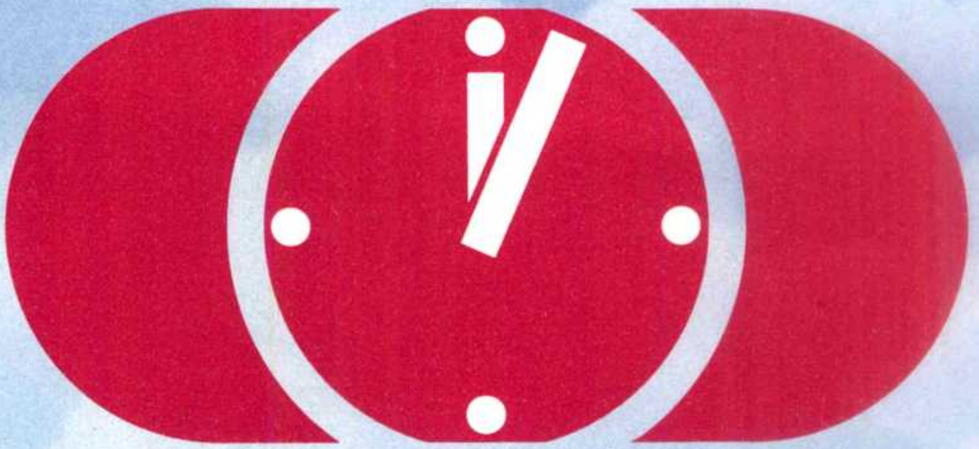
# 24 hour



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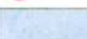
| Mild to moderate hypertension in the majority of patients. | |  | |
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*Br Heart J* 1986; 55: 227–30

# Percutaneous transluminal coronary angioplasty in unstable angina: comparison with stable angina

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SUMMARY Percutaneous transluminal coronary angioplasty was performed in 25 patients with unstable angina and in a similar group of 25 patients with stable angina. The frequency of single, double, and triple vessel disease was identical in each group. Technical success was achieved in 22 (81%) out of 27 attempts in those with unstable angina and in 14 (52%) out of 27 attempts in those with stable angina. Vessel occlusion occurred in nine patients, necessitating emergency bypass surgery in four. There was evidence of myocardial infarction in three patients in each group and one patient in the unstable group subsequently died. Twenty eight of 32 successfully treated patients were followed up by means of repeat coronary arteriography, exercise electrocardiography, and clinical assessment after a mean (SD) interval of 14 (7) months. There was angiographic evidence of restenosis in 32% (seven of 22) of lesions in the unstable group and 44% (four of nine) of lesions in the stable group. There were no late infarctions or deaths during the follow up period. These results support the growing evidence that angioplasty can be carried out safely and effectively in patients with unstable angina.

The risk of infarction and death is high in patients with unstable angina.[1] Excluding patients with main stem disease, most studies have shown similar infarct and mortality rates when such patients are treated medically or surgically.[2 3] Patients treated medically, however, are more likely to have severe symptoms during follow up and many eventually require operation for relief of incapacitating angina.

Percutaneous transluminal coronary angioplasty is a new treatment of obstructive coronary disease in which a specially designed balloon tipped catheter is introduced through a peripheral artery and inflated across an atherosclerotic plaque to relieve the obstruction. Successful angioplasty can relieve angina and improve objective signs of myocardial ischaemia.[4 5] Despite the growing experience worldwide with this technique, little information is available about its suitability in patients presenting with unstable angina. We report the efficacy and long term results of coronary angioplasty combined with medical management in selected patients with this condition.

## Patients and methods

Between November 1982 and April 1984, 25 patients with unstable angina and a similar group of 25 patients with stable angina presenting to three hospitals were deemed to be suitable for percutaneous transluminal coronary angioplasty. This group constituted 50 (89%) of the first 56 cases in which angioplasty was performed at our hospital. All patients with unstable angina had experienced either (*a*) worsening in frequency, severity, or duration of chest pain; or (*b*) severe episodes of prolonged pain at rest immediately before admission. Angioplasty was performed in these patients during the same hospital admission after initial management by bed rest and medical treatment including nitrates, $\beta$ blockers, and calcium antagonists. Serial electrocardiograms and enzyme estimations were performed to exclude fresh myocardial infarction.

Angiographic indications for angioplasty included high grade (>70% reduction of lumen diameter) accessible lesions in one or more major coronary vessels. Patients with left main stem disease, severe diffuse disease, total vessel occlusion, or involvement of major side branches were considered to be unsuitable as were those who were otherwise unfit

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Accepted for publication 25 November 1985

Table 1 *Patient description and results*

| *Data* | *Stable* | *Unstable* |
|---|---|---|
| No of patients | 25 | 25 |
| Mean age (years (SD)) | 53±7 | 53±8 |
| Males : females (%) | 76:24 | 68:32 |
| Mean duration of angina (months (SD)) | 34±53 | 7±10 |
| Previous infarction (No of patients) | 3 | 4 |
| Coronary disease (No of patients): | | |
| Single vessel disease | 12 | 12 |
| Double vessel disease | 9 | 9 |
| Triple vessel disease | 4 | 4 |
| Mean (SD) transstenotic gradient (mm Hg) | 55±16 | 60±13 |
| Mean (SD) diameter stenosis pre-angioplasty (%) | 85·4±9 | 85·1±8 |
| Number of attempted dilatations | 27 | 27 |
| Success (%) | 52 | 81 |
| Complications (No of patients): | | |
| Ventricular fibrillation | 5 | 1 |
| Vessel occlusion | 4 | 5 |
| Myocardial infarction | 3 | 3 |
| Death | 0 | 1 |
| Emergency operation (No of patients) | 1 | 3 |

for coronary artery bypass surgery. Informed consent was obtained from all patients after we had discussed their clinical and angiographic data with the cardiac surgeons. Angioplasty was performed as previously described.[6] All patients received nifedipine 10 mg orally before the procedure. After successful angioplasty heparin (20 000 units) was administered by continuous infusion for 24 hours and patients were subsequently discharged on aspirin 300 mg daily for six months.

We analysed and compared results for each group, using the $\chi^2$ test where appropriate.

## Results

Twenty seven dilatations were attempted in 25 patients in each group. Table 1 summarises the details. The average interval between admission and angioplasty in patients presenting with unstable angina was 11·5 days (range 1–58 days). A technically successful dilatation, defined as at least a 20% increase in lumen diameter, was achieved in 14 out of 27 attempts in patients with stable angina and in 22 out of 27 attempts in those with unstable angina. In 32 patients in whom angioplasty was successful, the mean (SD) diameter stenosis was reduced from 84 (8%) to 22 (22%) and the mean transstenotic gradient from 58 (13) to 17 (10) mm Hg (Fig). Angioplasty was unsuccessful in 18 patients, and this was mainly because severely stenotic segments (12 patients) could not be crossed. In three we were unable to approach the stenosis because of vessel tortuosity. After successfully crossing the stenosis in two patients, we were unable to improve the angiographic appearance or appreciably reduce the transstenotic gradient. One patient with unstable angina initially had a successful dilatation of a lesion of the proximal left anterior descending artery but subsequently occlusion of the distal vessel developed; this was presumably due to a dislodged thrombus. Four patients in whom failed angioplasty was associated with clinical deterioration had emergency bypass surgery; two of them had evidence of transmural infarction on subsequent electrocardiograms. Acute vessel occlusion occurred in nine patients and was associated with electrocardiographic and enzyme changes of infarction in five, despite emergency operation in two and repeat angioplasty in another. One patient in whom angioplasty was unsuccessful and uncomplicated had a myocardial infarction 12 hours later and since then

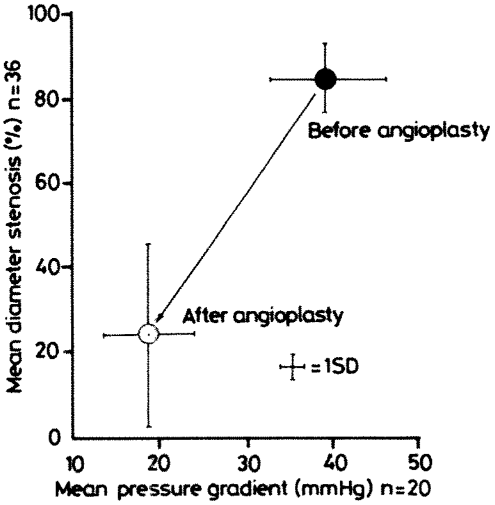

Figure *Pressure recordings across coronary stenoses in 36 successful dilatations.*

Table 2 *Site of attempted dilatation*

| *Angina* | *LADp* | *LADm* | *RCAp* | *RCAm* | *Circ* | *Total* |
|---|---|---|---|---|---|---|
| Stable | 10 | 12 | 2 | 2 | 1 | 27 |
| Unstable | 15 | 10 | — | 1 | 1 | 27 |

LAD, left anterior descending artery; RCA, right coronary artery; Circ, circumflex coronary artery; p, proximal to first septal perforator (LAD) or first anterior ventricular branch (RCA); m, mid-segment.

has been angina free. In one case failure to cross a mid-segment stenosis of the left anterior descending artery was associated with acute vessel occlusion and what initially appeared to be a small uncomplicated anterolateral infarct. We decided not to proceed to emergency operation. A week later this patient had an extension of his infarct with recurrent ventricular fibrillation. Progressive clinical deterioration followed and he died of cardiogenic shock and renal failure.

Follow up in 32 of the successfully treated patients (20 from the unstable group and 12 from the stable group) included clinical assessment, repeat coronary arteriography (28 patients), and exercise electrocardiography (26 patients). The mean interval between angioplasty and follow up arteriography was 14 (7) months (range 2–28 months). All except one patient, who presented with recurrent unstable angina after two months, were followed for at least five months (Table 3). Restenosis was defined as a loss of $>50\%$ of the previous gain in luminal diameter. Seven patients in the unstable group complained of chest pain on close questioning; four of them had restenosis. One patient presented with recurrent unstable angina and restenosis within two months and had coronary bypass surgery. Five patients in the stable group had recurrent chest pain, with restenosis in four.

There was angiographic evidence of restenosis in seven (32%) of 22 lesions successfully dilated and restudied in the unstable group and in four (44%) of nine lesions in the stable group. Three out of 11 patients with restenosis were free of symptoms and eight of them had negative submaximal exercise electrocardiograms. The four patients in the stable group who were not restudied are angina free. There were no late infarctions or deaths in either group during the follow up period.

Table 3 *Long term follow up in successfully treated patients*

| | *Stable* | *Unstable* |
|---|---|---|
| No of patients | 8 | 20 |
| Mean (SD) interval* (months) | 16 (6) | 14 (7) |
| Late deaths | 0 | 0 |
| Non-fatal infarction | 0 | 0 |
| Recurrent chest pain | 5 | 7 |
| Positive exercise test | 1 | 4 |
| Restenosis (No of lesions) | 4 | 7 |

*To repeat arteriography.

## Discussion

The optimal management of patients with unstable angina has been the subject of much discussion over the past 10 years.[7] A conservative approach may be appropriate when chest pain settles rapidly with medication.[8] Medical management alone is associated with a considerable risk of subsequent infarction and death,[9 10] and a high recurrence rate of severe angina during follow up. Twenty of our patients presented with crescendo angina while five had severe cardiac pain at rest. Ten patients had recurrent episodes of pain in hospital despite bed rest and medical treatment and thus belonged to a high risk subgroup. Mechanical intervention when the coronary pathophysiology is unstable might be expected to be more difficult and possibly more hazardous than in patients with stable angina. Our results suggest that this is not so. The success rate of angioplasty in patients with unstable angina was higher (81% *vs* 52%) than that in the stable group, while the frequency of serious complications such as vessel occlusion and myocardial infarction was similar in both groups. Table 1 shows that both groups were similar in terms of mean age, previous infarction, extent of coronary disease, and severity of stenosis before angioplasty. From the beginning of our programme the ratio of successful intervention in each group remained the same, implying that increasing experience and technological development do not explain the apparent difference in results. This difference may be explained in several ways. Firstly the frequency of severe stenoses affecting the proximal portion of the left anterior descending artery (Table 2) was higher in patients with unstable angina. This is the ideal site for attempted angioplasty.[11] These patients had had symptoms for a shorter time, perhaps indicating the presence of a rapidly evolving, soft, distensible lesion which may be associated with plaque rupture or thrombus formation or both. Such a lesion is more likely to allow passage of the balloon catheter and subsequent dilatation. There was evidence of distal embolisation in one patient with unstable angina after dilatation of a severe proximal stenosis. This seems to be a rare complication of angioplasty, but not an unexpected one if, as seems likely, fresh thrombus formation plays a part in the pathophysiology.[1,2]

The two groups comprised a large part (89%) of our initial experience with this technique. It is likely that with increased experience the success rate in the stable group will rise and the difference between the two groups will become less pronounced, as shown by Meyer *et al* in the only other published report in which the efficacy of angioplasty in stable and unstable angina has been compared.[13]

The total, that is, in hospital and late, infarct and mortality rates (12% and 4% respectively) in our patients with unstable angina who underwent angioplasty compare favourably with published results of similar patients treated medically or surgically.[2,3] Our results are slightly biased, however, by the fact that two patients had successful emergency bypass surgery without infarction after acute vessel occlusion had occurred during angioplasty. Others have shown similar mortality[14,15] and complication rates when operation and angioplasty are compared, whereas medical treatment alone is associated with recurrence of severe symptoms in 20–40% of patients during the first year of follow up.[2] Although on questioning seven (35%) of our patients complained of chest pain during follow up, three of them had no evidence of restenosis or important disease elsewhere to account for their symptoms. Angina, when it did recur, was usually mild, that is, grade I–II (New York Heart Association criteria), except for one patient who presented with recurrent unstable angina and required emergency bypass operation.

Exercise electrocardiography was surprisingly unhelpful in identifying those patients with restenosis. This is consistent with the recently reported findings of De Feyter *et al*[16] but we cannot account for this finding.

In conclusion, our work supports the observation that urgent coronary angioplasty combined with medical treatment can be performed safely and effectively in patients with unstable angina. In addition the nature of the pathophysiological processes in these patients may make them technically more suitable for this procedure than those with stable angina.

We thank Dr D Hogan for his invaluable help in carrying out this work.

This work was supported by a grant from the Irish Heart Foundation.

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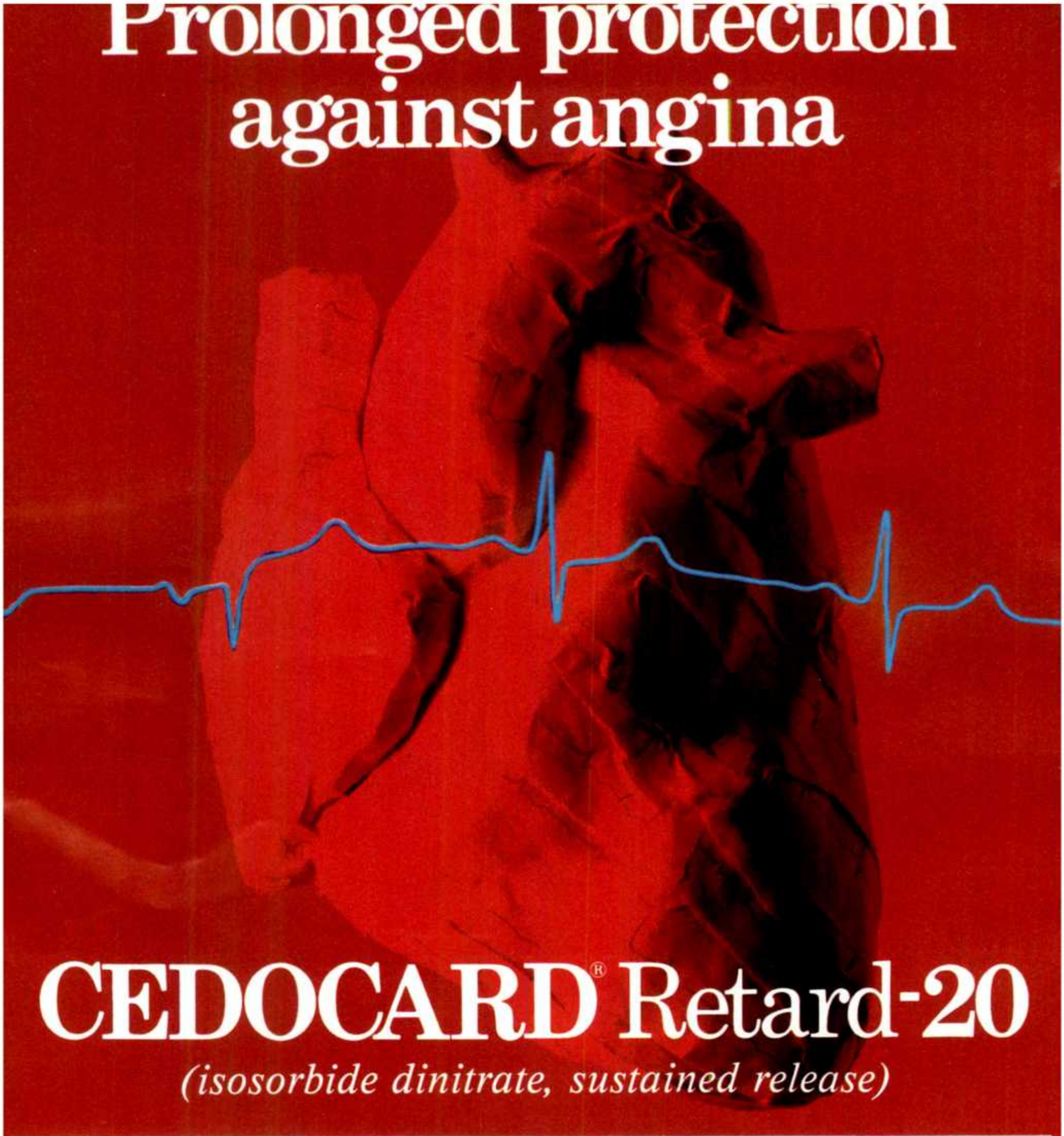

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# High dose intravenous streptokinase in acute myocardial infarction—short and long term prognosis

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SUMMARY Streptokinase (1 million international units) was given intravenously over 30 or 60 minutes to 50 patients four hours or less after the onset of acute myocardial infarction. All were aged $\leqslant$70 years and had 4 mm or greater ST segment elevation in anterior or inferior leads. Rapid (mean 95 min) ST segment resolution, which was taken to indicate reperfusion of the myocardium, occurred in 36 (72%) patients. In these 36 the average time from onset of symptoms to peak creatine kinase, creatine kinase MB, and myoglobin was 9·45 hours, whereas it was 17 hours in the 14 patients in whom indirect criteria did not indicate reperfusion. Reperfusion arrhythmias were invariably present and ventricular tachycardia developed in five patients and ventricular fibrillation in two. The infarct related artery was seen to be open in 28 (70%) of the 40 patients who had delayed coronary arteriography. The frequency of patency in the infarct related artery was no different in patients given streptokinase <2 hours or between 2–4 hours from onset of symptoms nor did it differ when streptokinase was infused over 30 or 60 minutes. Mean left ventricular ejection fraction was 57% in those with a patent infarct related artery and 48% in those with an occluded vessel. Eight patients subsequently underwent elective percutaneous transluminal coronary angioplasty after successful thrombolysis and six had coronary artery bypass grafting. There were nine in-hospital reocclusions of the infarct related coronary arteries. Two bleeding episodes occurred; one required transfusion. Five of the 50 patients died in hospital. All of them had had an anterior myocardial infarction; four had bifascicular block and one had right bundle branch block. During follow up, four patients died, two suddenly and two from reinfarction. During follow up (mean 15 months) the frequency of reinfarction, dyspnoea, and angina was low and there was no difference in the proportions of patients returning to work between those with an open infarct related artery and those with a closed infarct related artery.

Intravenous administration of high dose streptokinase to selected patients during the acute phase of myocardial infarction is a safe, effective, and practical method of thrombolysis. It must, however, be followed by coronary arteriography to select those patients in whom percutaneous transluminal coronary angioplasty or coronary artery bypass grafting will be helpful.

In most patients acute myocardial infarction is associated with an acute intraluminal coronary artery thrombosis on an atheromatous plaque.[1-4] The amount of necrotic muscle resulting from coronary artery occlusion is a major factor determining the outcome of acute myocardial infarction. Although recanalisation of a coronary artery may occur spontaneously,[5] restoration of anterograde flow in the occluded vessel by thrombolytic treatment may terminate or limit the ischaemic process and so reduce the amount of tissue death. At present, early reopening of an occluded infarct related vessel by thrombolysis appears to be the most promising approach in limiting infarct size.[6]

During acute infarction the area of acute necrosis

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Accepted for publication 3 December 1985

spreads from the subendocardial surface through to the subepicardial surface,[7 8] and experimental studies in dogs have shown that early interruption of this destructive advance is likely to offer the best prospect of salvage or recovery in the ischaemic myocardium.[9 10] Establishing reperfusion within four hours of complete ischaemia may result in important structural and functional recovery.[11 12] After four hours of complete ischaemia major improvement seems to be unlikely[11 12] and reperfusion in such cases possibly only helps to accelerate the decay of already irreversibly injured tissue. The extent of collateral flow, however, is likely to be a major determinant of the time course and final size of infarction in patients.[8]

Despite almost two decades of experience, the benefits and risks of administration of intravenous streptokinase in acute myocardial infarction remain to be established. Early randomised studies[13-15] gave equivocal results because populations were heterogenous, treatment was started too late (6–12 hours or more) after the onset of symptoms to be of any benefit, slower infusion times were used, and evidence of reperfusion was not recognised or was misinterpreted.

Intracoronary streptokinase given on average (SD) 4·3 (1·4) hours after acute myocardial infarction was associated with a 76% recanalisation rate in the infarct related artery.[16] When intravenous streptokinase was given on average 2·8 (1) hours after onset of symptoms, the same workers showed a recanalisation rate of 73%.[16] When intravenous streptokinase was given within six hours of myocardial infarction, early reperfusion, that is within one hour, occurred in 49% of patients.[17] In a similar group of patients Schroder found a patent infarct related artery in 84% at angiography four weeks later.[18] The intravenous route, which does not require emergency arteriography and so is more generally applicable, allows treatment to be started as soon as possible after the onset of symptoms.

We have evaluated the effects of high dose short term intravenous streptokinase in patients presenting within four hours of the onset of acute myocardial infarction and have followed their course after leaving hospital.

## Patients and methods

All patients were aged $\leqslant 70$ years, had had symptoms for $\leqslant 4$ hours, and showed an acute injury pattern on the electrocardiogram (that is $\geqslant 4$ mm ST segment elevation in two or more anterior or inferior electrocardiographic leads after pain relief). No patient had uncontrolled hypertension or a potential bleeding site. Those patients already on anticoagulants were excluded. Informed consent was obtained from all. No patient died between acceptance for the study and the administration of streptokinase.

Before treatment was started, blood was drawn for a complete blood count, platelet count, prothrombin time, partial thromboplastin time, fibrinogen, total creatine kinase, creatine kinase-MB, and myoglobin. A 12 lead electrocardiogram was recorded. Hydrocortisone (250 mg), given intravenously to prevent an allergic reaction to streptokinase, was followed immediately by a 100 000 IU bolus of streptokinase and then by an infusion of 900 000 IU in 100 ml of physiological saline. Infusion lasted 60 minutes in 20 (40%) patients and over 30 minutes in 30 (60%) patients. After the streptokinase infusion, heparin 40 000 IU was infused over 24 hours. The activated partial thromboplastin time was checked at two, four, eight, 12, and 24 hours after completion of streptokinase administration and the amount of heparin infused was adjusted daily in an attempt to maintain the activated partial thromboplastin time between 80 and 120 s. The infusion of heparin was continued until either delayed coronary arteriography was performed or circumstances dictated otherwise. After arteriography, if angioplasty was not considered, heparin was discontinued and either antiplatelet drugs or warfarin were given daily. After the end of the streptokinase infusion the electrocardiogram was recorded again and thereafter at 30 minutes, one, two, four, eight, 12, 16, and 24 hours with concurrent measurement of serum creatine kinase, creatine kinase-MB, and myoglobin concentrations. Thereafter electrocardiograms were recorded daily. Coronary arteriography was performed later by the Judkins's transfemoral technique in all except one patient in whom the brachial approach was used. Ejection fraction was assessed in the 30° right anterior oblique projection of the left ventriculogram.

Reperfusion of the myocardium or recanalisation of a recently occluded artery was recognised by (*a*) rapid decline ($\geqslant 3$ mm) of the ST segment injury current on the electrocardiogram; (*b*) early rise and peak ($\leqslant 12$ hours) in serum creatine kinase, creatine kinase-MB, and myoglobin levels; (*c*) the occurrence of specific reperfusion arrhythmias-ventricular extrasystoles, runs of idioventricular rhythm, ventricular tachycardia, or ventricular fibrillation; (*d*) luminal patency of infarct related artery demonstrated at coronary arteriography.

## Results

Thrombolysis was attempted in 50 patients (41 male and nine female) aged 37–69 (mean 57 years); 33 of

Table 1 *Peak creatine kinase (CK), creatine kinase-MB (CK–MB), and myoglobin (MB) and time taken to reach peak values in patients with an open infarct related artery and those with a closed artery*

| *Peak mean (SD)* | *Time to peak (h)** |
|---|---|
| Open artery | |
| CK 2337 (1580) U/l | 4–12 (8·5) |
| CK-MB 121 (88) U/l | 3–10 (7·45) |
| MB 2613 (3060) μg/l | 3–8 (6·5) |
| Closed artery | |
| CK 2105 (506) U/l | 9–24 (16) |
| CK-MB 87 (43) U/l | 7–18 (15) |
| MB 2664 (1936) μg/l | 6–13 (8) |

*Range (mean).

them had had an anterior infarction and 17 had had an inferior infarction. Nine had had previous myocardial infarctions. Streptokinase was administered on average 150 (range 35–240 min) after the onset of symptoms. Of the 50 patients, 36 (72%) showed indirect evidence of reperfusion. Rapid resolution of ST injury pattern by ⩾3 mm occurred in all 36 in an average time of 95 min (range 30–180 min) after the start of treatment. Serum creatine kinase, creatine kinase-MB, and myoglobin kinetics were accelerated in all those who showed ST segment improvement. Peak values were reached ⩽12 hours (mean 9·45 hours, range 3–12 hours) after onset of symptoms in the 36 patients showing rapid ST segment resolution. In those whose ST segments remained elevated (⩾4 mm) creatine kinase, creatine kinase-MB, and myoglobin values reached a peak 17·3 hours (range 6–24 hours) after the onset of symptoms. In these 14 patients indirect criteria were considered not to indicate reperfusion.

Forty patients, 25 with anterior infarction and 15 with inferior infarction, subsequently underwent delayed coronary arteriography. Of the 10 patients who did not undergo coronary arteriography, five had died in hospital, three had had overt reinfarctions with further chest pain, ST segment re-elevation, and a further rise in serum enzyme activity, and two showed evidence of initial large infarctions without indirect evidence of reperfusion. Thirty five patients underwent arteriography within 21 days (mean 14, range 6–21 days), four patients between 22–28 days, and one at one month after admission (this patient had developed a retroperitoneal haematoma during the initial hospital admission). Single vessel disease with ⩾70% stenosis was present in 18 (45%) patients, double vessel disease in 11 (27%), and triple vessel disease in six (15%). The remaining five had lesions with <70% stenosis. The artery supplying the infarct territory was patent in 14 (78%) of the 18 patients with single vessel disease, in six (54%) of the 11 patients with double, and in three (50%) of the six patients with important triple vessel disease. Eighteen had been given streptokinase over 60 minutes and in 11 (61%) of them the infarct related artery was open. Twenty two patients had streptokinase administered over 30 minutes and 17 (77%) of them had an open infarct related artery. These differences were not statistically significant.

Thus the infarct related artery was patent in 28 (70%) patients. Of these 28 open arteries, 19 (68%) were associated with anterior infarction and nine (32%) with inferior infarction. Concordance between direct and indirect evidence of reperfusion was very high: all patients whose myocardium was reperfused (that is had an open infarct related artery) had one or more reperfusion arrhythmias and in all except two serum enzymes peaked within 12 hours of the onset of symptoms. Enzyme release and the time to peak enzyme activities for those with an open infarct related artery were compared with values in patients with a closed infarct related artery (Table 1). There was no statistically significant difference between those with open and closed infarct related arteries for mean peak creatine kinase, creatine kinase-MB, or myoglobin. Time to peak creatine kinase, creatine kinase-MB, and myoglobin from onset of symptoms was earlier, however, in the group with the open infarct related artery than in the group with a closed infarct related artery. Eighteen patients received streptokinase within two hours of the onset of symptoms and in 13 (72%) of them the

Table 2 *Details of patients with re-occlusion*

| *Patient No* | *Initial and reinfarction sites* | *APTT at time of reocclusion (s)* | *Time of reocclusion* | *Angiography (infarct related artery)* |
|---|---|---|---|---|
| 1 | Anterior | — | Silent | 100% occluded |
| 2 | Inferior | 45 | Day 3 | No angiogram |
| 3 | Inferior | 60 | Day 4 | No angiogram |
| 4 | Inferior | 58 | Day 9 | 100% occluded |
| 5 | Inferior | — | Silent | 100% occluded |
| 6 | Anterior | 27 | Day 4 | 100% occluded |
| 7 | Anterior | — | Silent | 100% occluded |
| 8 | Anterior | 45 | Day 5 | No angiogram |
| 9 | Anterior | 34 | Day 5 | 100% occluded |

APTT, activated partial thromboplastin time infarct related artery was open. Twenty two received streptokinase between two and four hours after the onset of symptoms and in 15 (68%) the infarct related artery was open. Eleven had received streptokinase infusion over 60 min and 17 over 30 min.

Left ventricular ejection fraction at angiography was on average 57% (range 23–84%) in those with patent lumens and 48% (range 27–71%) in those with an occluded infarct related artery. This difference is not statistically significant. The ejection fractions were independent of the timing—that is whether arteriography was performed within or more than two weeks after treatment. In those who had reperfusion of the myocardium the average ejection fraction associated with inferior infarction was 64%, whereas in those with anterior infarction it was 57%.

Six (12%) of the 50 patients had had ventricular fibrillation before streptokinase administration. Five of these showed indirect evidence of reperfusion and two had open infarct related arteries at arteriography. Three had overt reinfarctions, and at arteriography in two the infarct related artery was closed. The sixth patient died in hospital. Early post-thrombolytic or reperfusion arrhythmias—idioventricular rhythm and late diastolic ventricular ectopic beats—were invariably present in patients with reperfusion of the myocardium. Five (10%) had ventricular tachycardia within four hours of streptokinase infusion, which required anti-arrhythmic treatment, and in all of them the infarct related artery was patent at angiography. Two patients had ventricular fibrillation within five hours of streptokinase (one had had it before treatment and later died in pump failure; in the second, the infarct related artery was patent at arteriography).

Six overt non-fatal reinfarctions with chest pain, ST segment elevation, and increases in serum enzymes occurred in hospital (Table 2). Three of these patients subsequently underwent arteriography and in all of them the infarct related artery was occluded. Three patients who had shown indirect evidence of reperfusion had occlusion of the infarct related artery at angiography (considered to be silent reinfarction) and all survived. Thus nine (18%) reocclusions (five anterior, four inferior) occurred in hospital. No patient received further streptokinase after initial treatment.

None of the patients appeared to be allergic to streptokinase. Two bleeding events occurred. One 69 year old woman had gingival oozing within two hours of streptokinase infusion. Activated partial thromboplastin time was 65 s. Heparin dosage was subsequently halved, but she had a reinfarction on the third hospital day when the activated partial thromboplastin time was 45 s. No blood transfusion was required. A 47 year old man developed a retroperitoneal haematoma on day nine after streptokinase and while he was on heparin infusion and his activated partial thromboplastin time was 120 s. Five units of blood were transfused.

Eight patients who had successful reperfusion of the myocardium had elective percutaneous transluminal coronary angioplasty because they had stenoses accessible to this technique. Two of these patients had single vessel disease, three had double vessel disease, and three had triple vessel disease. Angioplasty was only used for single lesions—four right coronary artery lesions of between 90% and 99% and four left anterior descending lesions of between 85% and 95% narrowing. Coronary artery bypass grafting was carried out in patients with high grade lesions who continued to have angina despite intensive medical treatment. Six patients underwent coronary artery bypass grafting—four had single vessel disease (70–90% narrowing), one double vessel disease (100% and 95%), and one triple vessel disease (95%, 100%, 95% lesions).

There were five (10%) in-hospital deaths (Table 3). All the patients had anterior infarction and three had had previous inferior infarctions (average age 60 years, range 43–69). The mean duration of symptoms before streptokinase administration was 136 min (range 120–160). On admission four had bifascicular block and one right bundle branch block and four had pulmonary oedema. None had indirect

Table 3 *Details of the patients who died in hospital*

| *Patient No* | *Sex/Age* | *Site of infarction* | *Conduction abnormality* | *Time from admission to death* | *Pulmonary oedema on admission* |
|---|---|---|---|---|---|
| 1 | Male, 68 | Anterior | RBBB+LAH | 33 h | + |
| 2 | Female, 69 | Anterior (old inferior) | RBBB | 21 days | + |
| 3 | Male, 54 | Anterior (old inferior) | RBBB+RPH | 4 h | 0 |
| 4 | Male, 68 | Anterior (old inferior) | RBBB+LAH | 3 h | + |
| 5 | Male, 43 | Anterior | RBBB+LAH | 5 h | + |

RBBB, right bundle branch block, LAH, left anterior hemiblock; RPH, right posterior hemiblock.

evidence of reperfusion nor did the conduction delay resolve in any after streptokinase; none had streptokinase antibodies since in all five serum fibrinogen fell significantly. None of these patients underwent coronary arteriography. Death occurred in three, four, five, 33 hours, and on day 21 after admission. All were in cardiogenic shock before death. Three necropsies were performed. Two patients had severe triple vessel disease (stenosing atheroma) with recent thrombi in the infarct related vessels, and the third patient had single vessel disease with a recent total occlusion of the infarct related artery (Interstitial oedema was present in the lungs in all three. Fibrosis and scarring of the inferior and posterior surfaces of the left ventricle was noted in two patients in keeping with previous infarction.)

Of the 45 patients who were discharged, 40 had had angiography. Excluding the 11 who had either percutaneous transluminal coronary angioplasty or coronary artery bypass grafting or both, important stenoses were found in 15 of the remaining 29 patients with single vessel disease, in seven with double vessel disease, and in three with triple vessel disease. The remaining four patients had <70% stenosis of one or more vessels. Six of the 15 patients with single vessel disease had 70–79% lesions and nine patients had 90–100% lesions; in 10 of these patients they were left anterior descending coronary artery lesions and in five patients they were right coronary artery lesions. Of the seven with double vessel disease, three had 70–79% and four had 90–100% lesions of the left anterior descending artery; six had narrowing of the right coronary artery (in one this was 70–79%, in another it was 80–89%, and in four it ranged from 90% to 100%); and one patient had 70% narrowing of the circumflex artery. All three with triple vessel disease had 90–100% narrowing of the left anterior descending artery and in all of them the right coronary artery was occluded; in three patents the circumflex artery was narrowed (70% in one and 90–95% in two).

Of the 45 patients discharged from hospital, 28 had an open infarct related artery at angiography and two of these died during follow up; 12 had a closed infarct related artery and two of these died during follow up. None of the five who did not have coronary angiography died. Of the four deaths, one patient, a 58 year old man, died suddenly at home 10 months after discharge. He had had an earlier myocardial infarction before the one during which streptokinase was given. At angiography he had single vessel disease with an occluded infarct related artery. A treadmill exercise test was not performed because his left ventricular ejection fraction was only 10%. He had no angina after leaving hospital and was being treated for congestive heart failure. The second patient was a man aged 57 years who also died suddenly at home 12 months after discharge. The predischarge angiogram showed double vessel disease (100% and 75% lesions) with a closed infarct related coronary artery. This patient achieved 10 minutes of exercise on the Naughton and Balke protocol. He did not have chest pain during the exercise treadmill test nor did the blood pressure drop or any arrhythmias develop. ST segment elevation occurred in the area of inferior infarction and there were reciprocal changes in the anterior leads. He had not had angina after discharge. Case 3 was a 52 year old man who died from a further infarction 10 months after discharge. At angiography he had single vessel disease with 80% narrowing. He had been symptom free, had had no treadmill exercise stress test, and no angina had occurred after discharge. Case 4 was a 47 year old man who died of left ventricular failure associated with a further infarction three months after discharge. Reinfarction occurred during a treadmill exercise stress test and the patient died despite emergency bypass operation. At previous angiography he had 95% narrowing of left anterior descending artery (open infarct related artery), the right coronary artery was occluded, and there was 99% narrowing in the circumflex artery. The patient had claimed to be symptom free. Only two patients had reinfarctions during follow up and both of them died.

During the 11–22 months (mean 15·5 months) of follow up 11 of the remaining 41 patients had angina (New York Heart Association grade I or grade II) Eight of those with angina (grade I) had an open infarct related artery on discharge. Of the remaining three, two had a closed infarct related artery on discharge and in one there was no predischarge angiogram. Of these 11 patients, six had single vessel disease with ≥70% stenosis, one had double vessel

Table 4 *Drug treatment of the 41 patients during follow up*

| | *Calcium antagonists* | *Nitrates* | *β blockers* | *Antiplatelet agents* | *Anticoagulants* |
|---|---|---|---|---|---|
| Open infarct related artery on discharge (26 cases) | 15 | 17 | 11 | 15 | 5 |
| Closed infarct related artery (10 cases) or no angiogram (5 cases) | 5 | 4 | 4 | 4 | 1 |

disease with ≥70% stenosis, one had double vessel disease, and two had triple vessel disease. One patient had a single vessel 50% stenosis and one had no angiogram. Thirty eight patients had no dyspnoea. Two patients were in New York Heart Association functional class I and one was in functional class II. Table 4 shows the drugs taken during follow up.

Fifteen of the 41 patients went back to full employment, 14 retired early, nine remained unemployed, and three became unemployed. There was no difference in the proportions of those going back to work between those in whom the infarct related artery was open and those in whom it was closed.

## Discussion

Experience with patients undergoing thrombolytic treatment with intracoronary streptokinase suggests that the infarct related artery is likely to be occluded in 80–90% of patients before treatment is started.[19] The major findings in our study were that intravenous high dose streptokinase is a quick, safe, and effective method of achieving thrombolysis in selected patients during the acute phase of myocardial infarction and that 70% of infarct related arteries were patent at angiography. These results compare favourably with other studies in which successful coronary artery recanalisation was achieved in about 75% of patients with myocardial infarction treated by intracoronary streptokinase.[20] Alderman *et al* in a randomised study of patients with myocardial infarction gave streptokinase within 3·5 hours of the onset of symptoms; the patency rate with intravenous administraton was 62% compared with 73% in those receiving it by the intracoronary route.[21] Mayer *et al* found that high dose intravenous streptokinase given an average of 2·77 (1·31) hours from the onset of symptoms gave a patency rate of 83% in the infarct related artery at follow up angiography.[22]

Delay, the critical issue determining successful outcome, is minimised by intravenous administration which has the advantage of earlier and easier application in virtually every medical care facility. All our patients had had symptoms for four hours or less and the successful outcome of treatment in those treated within two hours of onset of symptoms (72%) compared favourably with those who were treated after two hours (68%). Thus it would seem reasonable to administer streptokinase to patients within four hours of the onset of acute myocardial infarction when it is still possible to achieve successful thrombolysis. The shorter streptokinase infusion time of 30 minutes *vs* 60 minutes was not associated with a significant increase in achieving patency of the infarct-related artery (77% *vs* 61%).

Although the groups were too small to determine the statistical significance of any differences, it was our impression that thrombolysis was more effective in patients with single vessel than in those with double or triple vessel disease (78% *vs* 54% *vs* 50%). Many of these single vessel lesions are accessible to subsequent angioplasty. The occurrence of ventricular fibrillation before thrombolysis should not deter one from attempting to interrupt the natural evolution to complete infarction. Two of the six patients in this study who had ventricular fibrillation before treatment later showed successful recanalisation. In one the rhythm disturbance recurred during treatment. Nevertheless, if human ventricular fibrillation resembles animal ventricular fibrillation then the longer the interval before reperfusion of an occluded vessel is established the less likely is ventricular fibrillation to develop.[7] Five patients developed ventricular tachycardia within four hours of thrombolysis. All were treated with conventional antiarrhythmic agents, in none was the arrhythmia fatal, and in all the infarct related artery was patent on angiography. These results indicate that prehospital administration of streptokinase in acute infarction should be considered, so that delay may be avoided and reperfusion be achieved as early as possible. Certainly the potential development of serious ventricular arrhythmias outside hospital should not exclude this therapeutic option.

In this study indirect evidence of reperfusion as demonstrated by accelerated electrocardiographic evolution and peak serum enzyme kinetics correlated well with the subsequent angiographic verification of patency. Both these non-invasive variables are now recognised markers of reperfusion.[16 18 19 23 24] When they occurred with reperfusion arrhythmias (late diastolic ventricular premature beats and self-terminating idioventricular rhythm[25]) recanalisation of the infarct related artery was almost always found. This information is most useful when facilities for performing coronary angiography are not available, and a clinical decision on which patients should be referred to specialised centres for arteriography after thrombolysis has to be made.

Ventricular function is often used to gauge success after thrombolysis. None the less ejection fractions must be considered with caution because the assessment of left ventricular function immediately after reperfusion is unlikely to demonstrate the ultimate benefit of thrombolysis as myocardial stunning may take place early on.[12] Left ventricular function (as measured by ejection fraction) is less severely impaired after inferior infarction than after anterior infarction in patients not receiving thrombolytic agents.[26] In this study the average ejection fraction for those with inferior infarction was higher than that for patients with anterior infarction. In a randomised study by Khaja *et al* of intracoronary streptokinase *vs* placebo given within six hours of acute myocardial infarction no beneficial effect on left ventricular function was seen,[27] unlike the results of the randomised study reported by Anderson *et al* in which ventricular performance was significantly better in those receiving intravenous streptokinase at 2 8 (1) (mean (SD)) hours than in a historical control group.[16] In our study left ventricular ejection fraction averaged 57% in those where the infarct related artery successfully recanalised after treatment and 48% in those with artery occlusion at angiography. Although this difference was not statistically significant, the improvement of approximately 10% in ejection fraction recorded in our study in successfully treated patients accords with reports from other workers.[11] Improved ventricular performance leads to better long term survival. Fatal arrhythmias and pump failure are more likely to develop in patients with low ejection fractions after acute myocardial infarction.[26]

Vessels with residual stenotic cross sectional areas less than 0·4 mm$^2$ are at high risk for rethrombosis, whereas vessels with minimal cross sectional areas of $>0$ 4 mm$^2$ are unlikely to develop rethrombosis.[28] Harrison *et al* found that 50% of patients with residual lesions causing >90% area stenosis had reocclusion whereas no patient with lesions of <90% area stenosis had vessel reocclusion.[28] After streptokinase reperfusion, however, the residual size of the lumen may change over the subsequent days either because of resolution of coronary artery spasm or lysis of persistent thrombi or changes in the atheromatous plaque. The reocclusion rate in this study was 18% (nine of 50). In most, anticoagulation at the time of reocclusion was considered to be suboptimal or was proving difficult to control. In three of the nine patients indirect criteria suggested recanalisation; this was followed by reocclusion. This has been described by others.[29 30] Successful thrombolysis will not alter the underlying disease process and the tendency to rethrombosis is a great and an ever present risk.[31 32] With anticoagulation, however, the reocclusion risk is likely to be low. The interval coronary arteriogram should be performed as early as possible after thrombolytic intervention, however. None the less this does not imply that the longer the delay in performing coronary arteriography, the greater the likelihood of rethrombosis. Reocclusion in our series occurred throughout the post-thrombolytic in-hospital period as did arteriography. In many cases the results of coronary arteriography will dictate the further management in the short or intermediate term.[33 34] Percutaneous transluminal coronary angioplasty was performed in eight patients who had lesions accessible to this technique in an attempt to optimise initial therapeutic success and preserve vascular patency. Six underwent coronary artery bypass operation because they had high grade lesions with continuing angina despite intensive medical treatment.

Bleeding complications during the study were infrequent. One patient required a blood transfusion for a retroperitoneal haematoma, which was caused by the heparin infusion rather than streptokinase. No allergic manifestations were seen in response to streptokinase. Five (10%) patients died during hospital stay. All were in the high risk group—that is they all had anterior infarctions, three had had previous inferior infarctions, four had pump failure on admission, and all had conduction abnormalities which were not corrected after streptokinase infusion. None of these patients showed indirect evidence of reperfusion. All were in cardiogenic shock at the time of death, with pump failure and a terminal arrhythmia. Thus the adverse prognosis, well recognised in this particular group of patients, was not improved by attempted thrombolysis.

Four of the 45 patients who survived to leave hospital died (two suddenly, two reinfarction) during follow up. The mortality rate was not higher than expected. For the remaining 41 patients, follow up lasted 11–22 months (average 15 5 months). Anticoagulation should continue outside hospital in this group of patients, particularly in those with high grade lesions. During the follow up the incidence of reinfarction, angina, and dyspnoea was low, as has been found by other workers.[17] The proportion of those with an open infarct related artery who went back to work was no different from that in those with a closed infarct related artery.

Intravenous streptokinase administration in early myocardial infarction appears to be a promising, safe, and effective treatment which can be used by all medical intensive care facilities. In our patients modification of the early course by successful thrombolysis meant that other measures to preserve vascular patency could subsequently be used during acute hospital stay and follow up. Successful thrombolysis will not modify the underlying coronary artery disease, and streptokinase should not be viewed as a therapeutic "magic bullet"; adjuvant treatment with agents designed to assist in myocardial salvage are currently being explored as are second generation fibrin-specific thrombolytic enzymes such as anisoylated plasminogen—streptokinase complex (BRL 26921)[35] or recombinant tissue type plasminogen activator.[36–41]

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# Treatment of angina pectoris with nifedipine and atenolol: efficacy and effect on cardiac function

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SUMMARY The antianginal effects of nifedipine 20 mg three times a day and atenolol 100 mg once a day singly and in combination were investigated in 16 patients with angina pectoris. The amount of work that could be done before angina and ST depression appeared was significantly increased by atenolol and the combination but not by nifedipine. At peak exercise the number of leads on a 16 point precordial electrocardiogram map that demonstrated $\geqslant 1$ mm ST segment depression was significantly reduced from a mean (SD) of 5·0 (0·4) on placebo to 3·7 (0·6), 2·8 (0·4), and 2·3 (0·7) on nifedipine, atenolol, and the combination respectively. Mean resting left ventricular ejection fraction, assessed by gated radionuclide ventriculography, did not change during any active treatment phase but increased significantly during exercise only on nifedipine and the combination.

The nifedipine/atenolol combination was the most effective treatment, and the data suggest that nifedipine may be used to best advantage in combination with a beta blocker.

Despite the introduction of calcium antagonists, beta adrenoceptor blockers remain the standard treatment for chronic stable angina pectoris in the United Kingdom. But the differing and possible complementary actions of beta blockers and calcium antagonists suggest the possibility of a beneficial drug interaction; indeed several studies of the combination of nifedipine or verapamil and beta blockers indicate an additive effect.[1-3]

Concern has been expressed about the possible depressant effects of this combination on cardiac function, however,[4-6] and, theoretically, reduction of sympathetic stimulation by beta blockade together with the intrinsic negative inotropic effect of calcium antagonism could depress myocardial contractility despite the peripheral vasodilating effect of the latter.

We have investigated the antianginal effects of a calcium antagonist (nifedipine) and a beta blocker (atenolol) singly and in combination on symptoms, exercise induced ischaemia, and left ventricular function.

## Patients and methods

### PATIENTS

We recruited sixteen male patients from the cardiology clinic of the Western Infirmary, all of whom had had chronic effort related angina pectoris with a stable pattern of symptoms for at least 3 months; none had pain at rest. The mean (SE) age of the group was 56 (2) years (range 45–63). All had an unequivocally positive exercise test for ischaemia ($\geqslant$0·1 mV ST segment depression for 80 ms after the J point) at the end of a two week placebo run-in period, during which all other antianginal medication had been withdrawn. Coronary arteriography showed coronary artery disease in all patients; 10 had triple, three had double, and three had single vessel disease. Eight had had a previous myocardial infarction and six patients were cigarette smokers who did not change their habit during the study period.

Exclusion criteria included chronic obstructive airways disease, blood pressure >160/100 mm Hg on no treatment, myocardial infarction within the previous 3 months, peripheral vascular disease, and previous congestive cardiac failure or pronounced conduction abnormalities on the electrocardiogram.

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Written consent was obtained from all patients and the study was approved by the ethical committee of the Western Infirmary.

### TRIAL DESIGN

There were four treatment periods each lasting 3 weeks and comprising placebo, nifedipine 20 mg three times a day, and atenolol 100 mg once daily singly and that combination. The order of administration was determined by a balanced latin square, and use of the double dummy technique ensured that all treatments were visually identical.

### SUBJECTIVE ASSESSMENT

Patients completed diary cards for anginal frequency and glyceryl trinitrate consumption and they were instructed to follow their normal daily routine throughout the period of the trial; moreover patients were instructed to use glyceryl trinitrate to treat acute attacks of angina (but not dyspnoea) and were asked not to take it prophylactically.

### OBJECTIVE ASSESSMENT

Supine bicycle exercise was carried out on two separate occasions, to record an exercise precordial map and to assess cardiac function by gated radionuclide ventriculography.

### EXERCISE PRECORDIAL MAPPING

Exercise was performed on an electronically braked bicycle ergometer, and was started at 25 W. The workload was increased by 25 W every 3 minutes. Each patient was allowed to exercise to his maximum; the end points were severe chest pain, dyspnoea, intolerable fatigue, important arrhythmia, or fall in blood pressure. Immediately after exercise, ST segment change was recorded on a 16 point precordial electrocardiograph map.[7] Heart rate and blood pressure were recorded throughout the test.

### RADIONUCLIDE VENTRICULOGRAPHY

The blood pool was visualised by in vivo labelling of the patient's red blood cells with 800 mBq of technetium-99m. Scintigraphic images were obtained with a single crystal gamma camera (Ohio series 100) fitted with a high resolution parallel hole collimater interfaced to a Varian computer. Patients were studied while they were supine and imaging was carried out in the left anterior oblique projection at an angle that allowed optimum separation of the right and left ventricles and showed minimal interventricular septal thickness (generally 35–45° left anterior oblique); a 10–15° caudal tilt was applied to allow image separation of the left atrium from the left ventricle and this position was kept constant for each patient throughout the study.

Electrocardiogram gated equilibrium data were collected at rest for three minutes and during the last two minutes of supine bicycle exercise at the maximum workload achieved during the placebo run-in period. The global left ventricular ejection fraction was calculated from the standard formula: end diastolic counts—end systolic counts/end diastolic counts—background counts using a peridiastolic background area along the left ventricular free wall.

Statistical analysis was performed by Student's paired *t* test unless stated otherwise.

## Results

### SUBJECTIVE ASSESSMENT

When compared with placebo results the frequency of angina was reduced significantly by nifedipine ($p<0{\cdot}05$) and atenolol ($p<0{\cdot}02$) singly and in combination ($p<0{\cdot}005$). Glyceryl trinitrate consumption was reduced by atenolol ($p<0{\cdot}02$) and the combination ($p<0{\cdot}01$), but during the nifedipine period this did not reach statistical significance (Fig. 1).

### OBJECTIVE ASSESSMENT

*Exercise precordial map*

There was no significant increase in total work done during treatment with nifedipine or atenolol when compared with placebo; only the combination significantly increased the total work done (mean (SE)) from 44 (6) to 51 (7) kJ ($p<0{\cdot}05$). Both atenolol and the combination significantly increased the work done to the onset of angina and to the onset of ST segment depression ($p<0{\cdot}05$ and $p<0{\cdot}02$ for atenolol and $p<0{\cdot}005$ and $p<0{\cdot}02$ for the combination respectively, by log rank analysis)[8] All active treatments reduced both the frequency of angina during exercise and the development of ST segment depression (Fig. 2). Angina pectoris was the limiting symptom in 12, eight, three, and one of the patients on placebo, nifedipine, atenolol, and the combination respectively.

Immediately after exercise the mean (SE) number of leads showing $>1$ mm ST segment depression was reduced from 5·0 (0·4) on placebo to 3·68 (0·6) ($p<0{\cdot}005$), 2·81 (0·4) ($p<0{\cdot}005$), and 2·25 (0·7) ($p<0{\cdot}005$) on nifedipine, atenolol, and the combination respectively. The mean (SE) total ST segment depression (mm) was reduced from 8·75 (1·5) on placebo to 7·0 (1·9) (NS), 4·2 (1) ($p<0{\cdot}001$), and 3·87 (1·5) ($p<0{\cdot}005$) on nifedipine, atenolol, and the combination respectively.

Resting heart rate (mean (SE)) did not change on nifedipine (68 (2) to 71 (2) beats per minute), whereas both atenolol and the combination lowered resting heart rate significantly and to the same extent

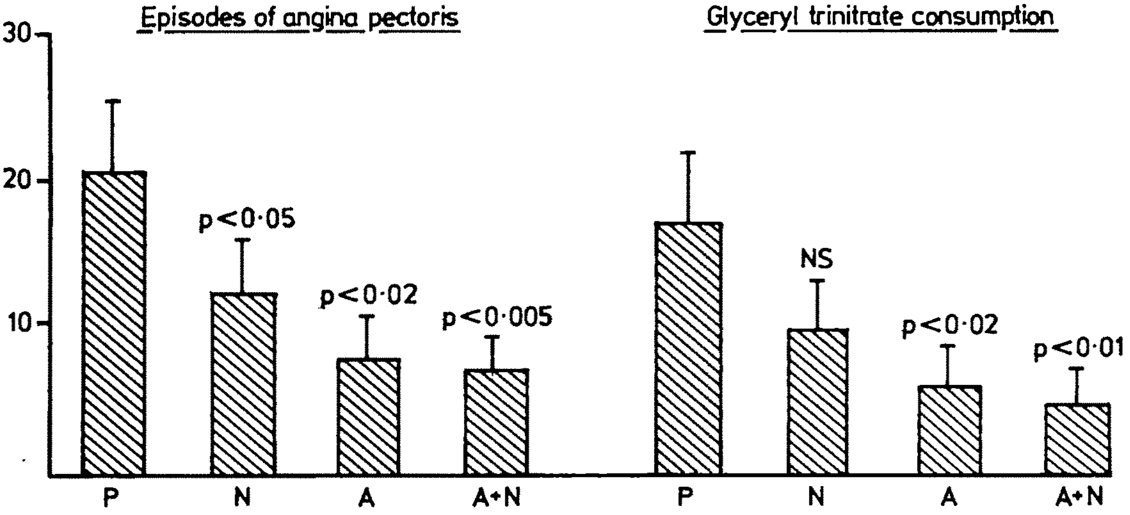

Fig. 1 *Frequency of angina pectoris and glyceryl trinitrate consumption during each three week treatment period; values are mean (SE). P, placebo; N, nifedipine; A, atenolol; A+N, combination.*

(54 (2) and 54 (2) beats per minute, $p<0\cdot001$). During exercise there was no significant difference in the peak rate pressure product (mean (SE)) on nifedipine and placebo (230 (13) *vs* 234 (15) × 100) but there was a highly significant reduction on atenolol and the combination (177 (8) and 174 (11) × 100, $p<0\cdot001$).

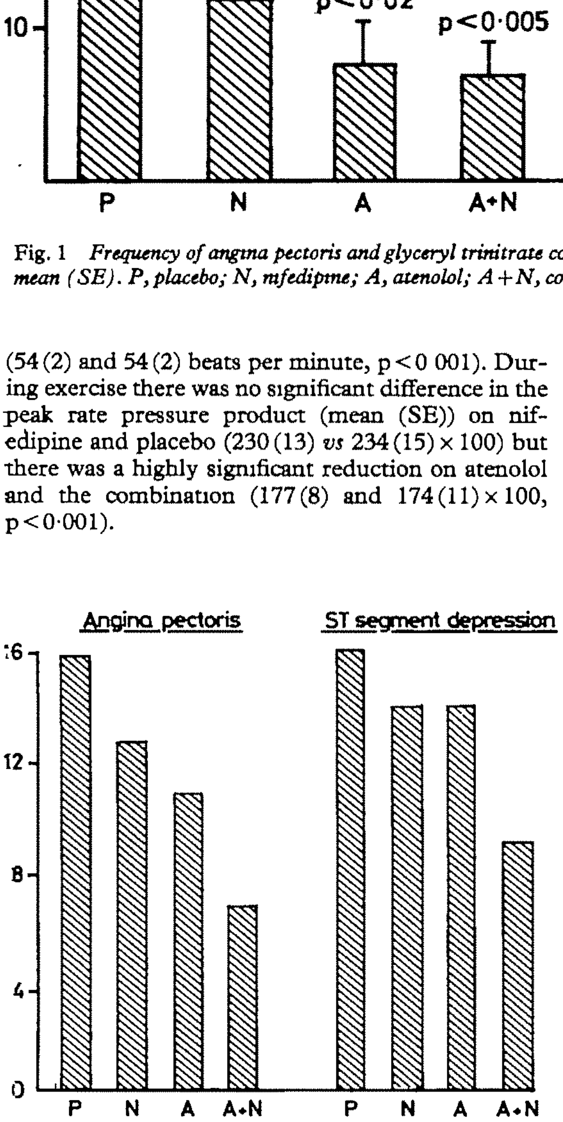

Fig. 2 *Number of patients developing angina pectoris or ST segment depression at maximum exercise. See legend to Fig. 1 for abbreviations.*

There were no deleterious effects on cardiac rhythm or conduction during any treatment phase.

RADIONUCLIDE STUDIES

Mean resting ejection fraction did not change significantly on any of the active treatment phases (Table). But when individual values were examined there was a correlation between the change in ejection fraction on combination treatment and the resting value on placebo (Fig. 3); in those patients with higher resting ejection fraction there was a fall, while in those with lower resting placebo values there was a slight rise; this was not evident when nifedipine or atenolol was given alone. During the exercise scan 14, 11, three, and one patients developed angina on placebo, nifedipine, atenolol, and the combination respectively; during both nifedipine and combination treatment there were statistically significant rises in left ventricular ejection fraction on exercise (Table).

The normal response of left ventricular ejection fraction to maximum dynamic exercise in our laboratory is a rise $\geqslant 7\%$. On placebo four (25%) patients had a normal response despite the presence of angina in three, while on nifedipine eight (50%) had a normal response despite the presence of angina in six; on atenolol only one (6%) patient had a normal rise in left ventricular ejection fraction despite 13 of the 16 patients being free of angina; on the combination six (40%) patients had a normal rise in left ventricular ejection fraction and only one patient developed angina (Table).

Table *Left ventricular ejection fraction (LVEF) response to dynamic exercise in the presence or absence of angina pectoris at time of acquisition. Mean (SE)*

| | *Placebo* | *Nifedipine* | *Atenolol* | *Combination* |
|---|---|---|---|---|
| Resting LVEF | 60 (2) | 60 (2) | 60 (2) | 58 (1) |
| Exercise LVEF | 63 (2) | 65 (3)<br>p<0 02 | 61 (2) | 62 (2)<br>p<0 005 |
| Angina pectoris during exercise | 14 | 11 | 3 | 1 |
| Normal exercise LVEF | 4 | 8 | 1 | 6 |
| Normal exercise LVEF despite angina | 3 | 6 | 1 | 1 |
| Normal exercise LVEF without angina | 1 | 2 | 0 | 5 |

## Discussion

In a previous double blind placebo controlled study of identical design nifedipine enhanced the antianginal effect of propranolol but when given alone it was less effective than the β blocker.[1] In general the present study confirms these findings for both nifedipine and atenolol given singly or in combination. Although the mode of action of β blockers in alleviating myocardial ischaemia by blunting the heart rate and blood pressure responses to exercise seems clear, the mechanism of action of nifedipine in exercise induced ischaemia is less obvious. Principally nifedipine is a vasodilator and it could act either by increasing coronary blood flow or by reducing myocardial oxygen consumption through its favourable effect on left ventricular afterload.[9-11] In a clinical trial these effects are difficult to separate and the balance of effects on the coronary and peripheral circulations cannot be determined with certainty. If an increase in coronary blood flow had occurred in our patients then the severity of ischaemia at any given rate pressure product would have been less. Nifedipine did not prolong exercise duration or reduce the rate pressure product when compared with placebo but there was a modest reduction in the severity of ST segment depression at maximum exercise. Thus, these data do not exclude a small beneficial effect on coronary blood flow. But in patients with atheromatous coronary artery disease and effort related angina the most important antianginal effect may be reduction of myocardial oxygen consumption in relation to total external work done. It is not surprising therefore that atenolol, which considerably reduced the rate pressure product, had greater effects on exercise induced ischaemia than did nifedipine.

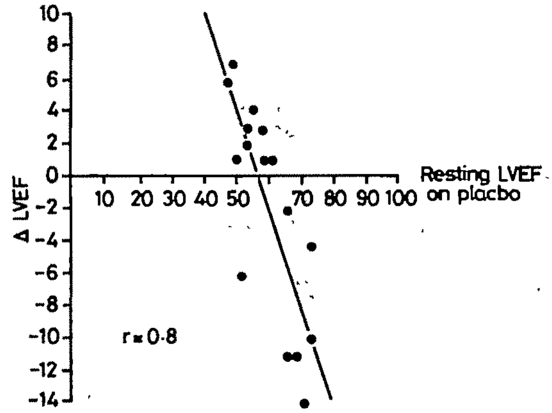

Fig. 3 *Change in resting left ventricular ejection fraction (ΔLVEF) during combination therapy. ΔLVEF equals result on combination minus result on placebo.*

Although hypotension and left ventricular failure have been described in anecdotal reports,[12-14] objective studies in which nifedipine was given to patients already established on a β blocker have been reassuring.[15-17]

The principal aim of the present study was to investigate in a double blind study the long term effects of this combination in patients with unimpaired left ventricular function before treatment. We assessed this by radionuclide ventriculography both at rest and during exercise and we have shown that at rest there was no significant change in the mean left ventricular ejection fraction during any treatment period. The normal response of left ventricular ejection fraction to dynamic exercise is a rise of at least 5%[18-20] and in patients with coronary heart disease failure to rise implies exercise induced myocardial ischaemia. Antianginal treatment, by preventing the development of ischaemia, might be expected to allow a normal response to exercise. But in our patients there was no improvement in left ventricular ejection fraction on atenolol during dynamic exercise, despite the presence of angina pectoris in only three patients. In normal subjects β blockade impairs the ejection fraction response to exercise[21 22] whereas in controlled studies in patients with ischaemic heart disease both attenuation and enhancement have been reported.[23-25] If left ventricular ejection fraction falls considerably on exercise because of severe ischaemia, prevention of this by β blockade would be expected to improve the ejection fraction response. But if ischaemia is mild as in our patients, then only a failure of the ejection fraction to rise normally on placebo would be expected, with little change on $\beta$ blockade.

Only on nifedipine and the combination was there a statistically significant rise in exercise left ventricular ejection fraction. On nifedipine this occurred despite the presence of angina in most patients. Possibly the reduction of left ventricular afterload induced by nifedipine allowed a rise in left ventricular ejection fraction despite the presence of myocardial ischaemia. On the combination the rise in left ventricular ejection fraction was associated with an almost complete abolition of angina pectoris which may have been due to the dual effects of afterload reduction induced by nifedipine and the abolition of myocardial ischaemia by atenolol.

In summary, the combination of nifedipine and atenolol was the most effective antianginal treatment in this group of patients. In addition on the combination, five patients had a normal left ventricular ejection fraction response to dynamic exercise together with the absence of angina pectoris. The combination was well tolerated and in those four patients who experienced a significant fall in left ventricular ejection fraction on the combination there was no clinical or symptomatic evidence of cardiac failure.

We conclude that the combination of atenolol and nifedipine is a safe and effective treatment of angina pectoris and is superior to either atenolol or nifedipine alone in patients with stable exertional angina pectoris. Indeed our data suggest that nifedipine may be used to best advantage in combination with a $\beta$ blocker rather than as a single agent. These results should not be extrapolated to other calcium antagonists or to patients with poor left ventricular function.

I N F was supported by a grant from the British Heart Foundation.

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*Br Heart J* 1986; 55: 246–52

# Left ventricular function during isometric hand grip and cold stress in normal subjects

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SUMMARY Both isometric exercise and cold stress have been suggested as alternatives to dynamic exercise for the detection of obstructive coronary artery disease. A non-imaging nuclear probe was used to measure left ventricular ejection fraction and relative left ventricular volumes continuously during both of these stress tests in 24 normal subjects. There was a significant fall in left ventricular ejection fraction within 15 seconds of subjects starting a two minute isometric hand grip test at 50% maximal voluntary contraction, with a mean (SE) maximal fall of 10% (1·8) after 90 seconds. During two minutes immersion of the hand and wrist in iced water left ventricular ejection fraction fell significantly within 30 seconds with a mean maximal fall of 7% (1·7) after one minute. Nine subjects underwent repeat tests under identical conditions approximately two weeks later. The standard error of the change in ejection fraction on two occasions was 5·4% at rest, 7·0% at the peak of isometric exercise, and 4·8% at peak cold stress.

These results indicate that the reproducibility of both of these stress tests is acceptable when they are performed under carefully controlled conditions. The resulting changes in ejection fraction are transient, however, and moreover depend upon the choice of stress protocol. The discrepancies between published reports of such studies in coronary artery disease may be mainly due to methodological differences, and neither test is likely to be of sufficient discriminative ability to distinguish between individuals with obstructive coronary artery disease and normal subjects.

There are similarities between the cardiovascular responses to isometric exercise and cold stress, and both have been advocated for the detection of obstructive coronary artery disease.[1 2] Isometric exercise in normal subjects increases blood pressure by 30–35%, which together with an increase in heart rate produces a pronounced increase in the rate-pressure product. Cutaneous cold stimulation leads to a rise in blood pressure of 20–25% with little change in heart rate, although cold stress may also affect myocardial blood flow through an alteration in coronary artery tone.[3 4] Left ventricular function during both these interventions can be assessed non-invasively by radionuclide angiography, but the reported results have been conflicting.[5-7] It is possible that some of the discrepancies have arisen as a result of differing patient selection, but there are also considerable methodological differences in the reported studies. In this study we set out to investigate the factors which may be important in determining the response of the left ventricle to these two stress tests. We used a non-imaging nuclear probe (Nuclear Stethoscope, Bios. Inc.) that allows continuous monitoring of precordial radioactivity from a $^{99m}$Tc labelled blood pool, to measure left ventricular ejection fraction and relative left ventricular volumes and to establish the temporal relation between these and other haemodynamic variables. We have also examined the reproducibility of the responses and the effect of differing isometric and cold stress protocols.

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Accepted for publication 4 November 1985

## Patients and methods

Twenty four male volunteers (mean age 32 years, range 25–43 years) took part in this study. All gave their informed consent and the study was approved by the hospital's ethical committee. Volunteers were screened by a full clinical examination and resting and symptom limited treadmill exercise testing; none had a history of cardiac disease.

### STRESS PROTOCOL

After 30 minutes of supine rest each subject performed isometric exercise with a hand grip dynamometer held at 50% of maximum voluntary contraction for two minutes. Five subjects also performed isometric exercise at 33% of maximum voluntary contraction for three minutes. Subjects were asked to count out aloud during isometric exertion and were observed closely for any tendency to perform a Valsalva manoeuvre. A cold stress test was performed by immersing a hand and wrist in iced water for two minutes. In five of these subjects the cold stress test was repeated with an immersion period of three minutes. Blood pressure was recorded every minute during stress and after three and five minutes of recovery by means of indirect auscultatory techniques, and heart rates were recorded from the cathode ray tube of the nuclear probe. After an average of two weeks (range 1–4) nine subjects underwent an identical programme of stress testing to establish the reproducibility of the responses.

### RADIONUCLIDE TECHNIQUE

The blood pool was labelled in vivo with stannous pyrophosphate (Pyrolite, New England Nuclear) followed 30 minutes later by 200 mg of sodium perchlorate and 740 MBq of ${}^{99m}$Tc. We used established routines to position the nuclear probe over the left ventricle.[8–10] Background activity was determined at the beginning of the investigation and before each intervention. The background and left ventricular regions of interest were marked and the probe was held in position during all interventions to limit errors due to movement. The background activity was also recalculated and corrected if necessary after one minute of each stress test in 14 subjects.

In 19 subjects multiple electrocardiogram gated left ventricular time-activity curves were generated at rest and at peak stress. In the gated mode 10 000 counts per 10 ms were collected to obtain a gated left ventricular time-activity curve with a standard deviation of 1% caused by radioactive decay.

### CONTINUOUS MEASUREMENT OF LEFT VENTRICULAR TIME-ACTIVITY CURVES

A continuous analogue signal representing the time course of activity was also obtained from the nuclear probe. The pulse output of the photomultiplier preamplifier was taken directly to an external pulse amplifier (Ortec Model 485) and thence to a rate meter (Ortec 441) whose time constant was set at 50 ms. The analogue voltage output of this rate meter was passed, unfiltered, to a galvanometric pen recorder (0–75 Hz bandwidth; Watanabe Linearcorder Series V). By this means, the nuclear probe's own ratemeter and filters were bypassed, so that the signal reaching the chart recorder was known to be free of important distortion. The background counts were also plotted on the chart recorder before and during each test.

The recordings from 16 subjects were later analysed by hand measurement of 15 beats after the initial 15 seconds and then every 30 seconds. Left ventricular ejection fraction was calculated for each cardiac cycle and averaged to produce a value which was expressed to an accuracy of one ejection fraction unit. Relative end systolic volume, end diastolic volume, and stroke volume were also calculated every 30 seconds, and serial changes were expressed as a percentage of the resting values.

### STATISTICAL METHODS

Ejection fractions at rest and peak of cold stress or isometric hand grip were compared by Student's *t* test (two tailed). Ejection fraction, heart rate, and blood pressure data obtained by continuous recordings were analysed by analysis of variance. Dunnett's *t* test was then used to compare resting values with each of the subsequent time points. Repeat measurements in the same subjects to assess reproducibility were analysed by three way analysis of variance.

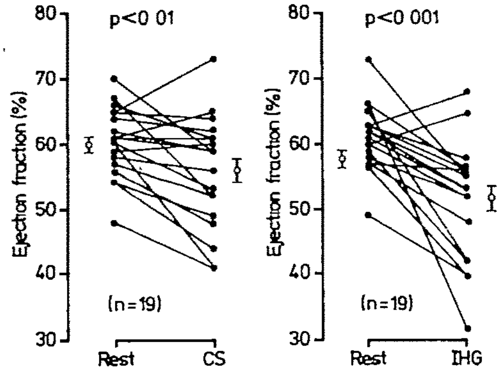

Fig. 1 *Individual changes in left ventricular ejection fraction from rest to peak cold stress (CS) and peak isometric handgrip (IHG). Mean (SE) is indicated.*

## Results

The mean (SD) count rate at rest was 4478 (599) counts/50 ms and the background counts were 57 (4)% of the mean count rate. Background counts increased by 5 (11)% during isometric exercise and by 3 (8)% during cold stress. Neither of these differences was statistically significant.

Fig. 1 shows the individual responses of left ventricular ejection fraction measured in the gated mode at rest and at the peak of both interventions. The mean (SE) resting left ventricular ejection fraction was 60 (1 2) before cold stress and fell to 56% (1·9) after two minutes, a mean fall of 4·5% ($p < 0{\cdot}01$). Before isometric hand grip, the resting left ventricular ejection fraction was 61% (1·1); this fell to 52% (2·0) after 2 minutes hand grip, a mean fall of 9·3% ($p < 0{\cdot}001$).

Measurement of the mean ejection fraction after 15 seconds and then every 30 seconds showed that cold stress produced a significant fall in ejection fraction after 30 seconds with a mean maximal fall of 7% occurring after one minute (Fig. 2). The ejection fraction subsequently increased but was still 6% below the resting value after two minutes. The recovery from cold stress was protracted; and left ventricular ejection fraction had still not returned to baseline levels after five minutes.

In contrast, isometric exercise (Fig. 3) produced a significant fall in ejection fraction after 15 seconds, reaching a nadir after 90 seconds. The recovery phase after stopping the hand grip was more rapid than with cold stress and the mean values were not significantly different from baseline at three minutes with an overshoot at five minutes. The fall in ejection fraction induced by isometric hand grip was significantly different from that induced by cold stress only after 90 seconds of stress ($p < 0{\cdot}05$).

Cold stress did not produce a significant change in mean heart rate. The maximum rise in blood pres-

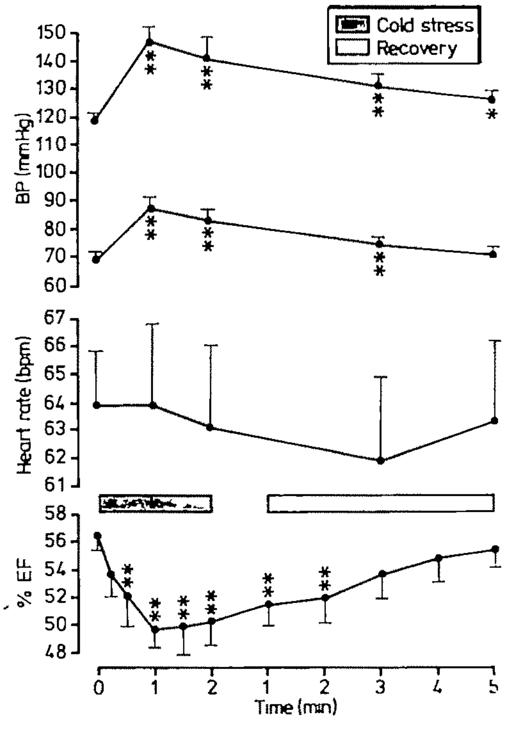

Fig. 2 *Mean (SE) response of systolic and diastolic blood pressure (BP), heart rate, and ejection fraction (EF) to two minutes' cold stress (n = 15). *p < 0 05, **p < 0 01 when compared with value at rest.*

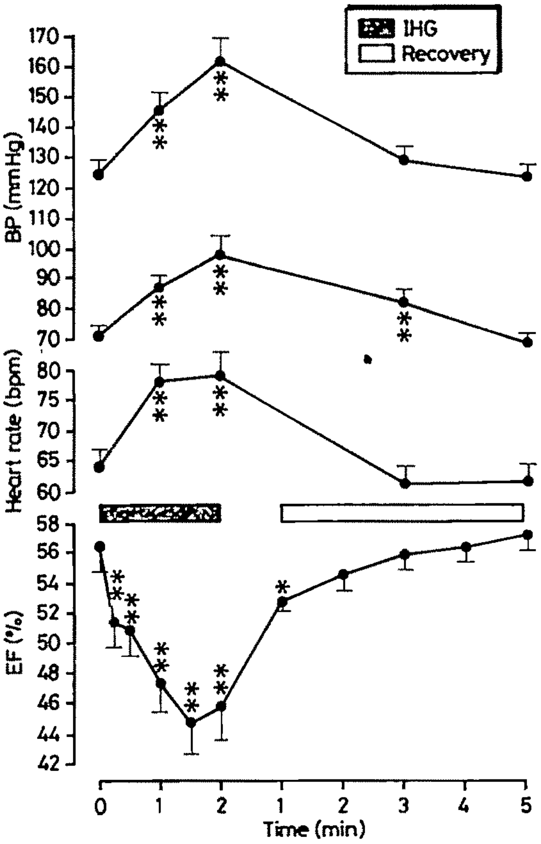

Fig. 3 *Mean (SE) response of systolic and diastolic blood pressure (BP), heart rate, and ejection fraction (EF) to two minutes' isometric hand grip at 50% maximum voluntary capacity (n = 15). *p < 0 05; **p < 0 01 when compared with value at rest.*

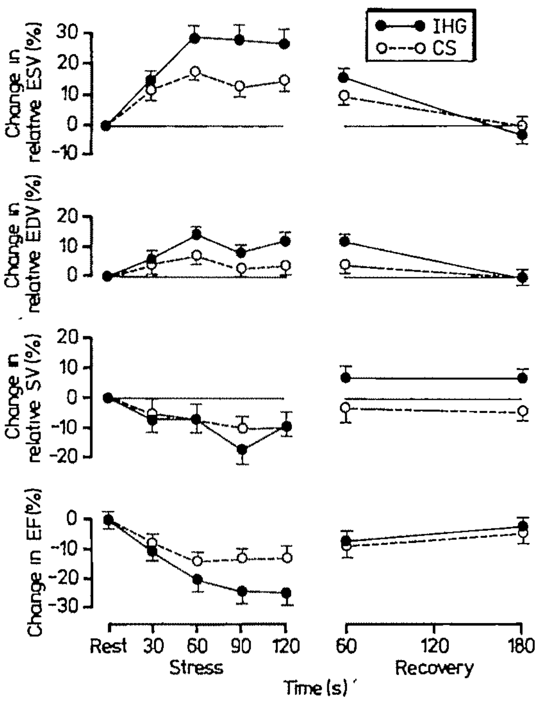

Fig. 4 *Mean (SE) percentage change in relative end systolic volume (ESV), end diastolic volume (EDV), stroke volume (SV), and ejection fraction (EF) during two minutes' isometric hand grip (IHG) and cold stress (CS).*

sure occurred after one minute and therefore occurred at the same time as the maximum fall in ejection fraction. Isometric exercise produced a significant increase in heart rate and a pronounced increase in the blood pressure with a maximum measured rise after two minutes.

In order to obtain an estimate of changes in relative left ventricular volumes, changes in total counts were assumed to be proportional to changes in volume. Figure 4 shows the percentage change from rest in relative end systolic volume, end diastolic volume, stroke volume, and ejection fraction. Isometric exercise produced a maximum increase of 29% in end systolic volume and 14% in end diastolic volume ($p<0{\cdot}001$) with a maximum decrease in stroke volume of 17% and ejection fraction of 24% ($p<0{\cdot}001$). Cold stress induced a maximum increase of 18% in end systolic volume ($p<0{\cdot}001$) and 7% in end diastolic volume ($p<0{\cdot}01$) and a maximum fall of 10% in stroke volume and 14% in ejection fraction ($p<0{\cdot}01$).

The response of the left ventricular ejection fraction to two and three minutes of cold stress is shown in Fig. 5. The mean fall in ejection fraction was identical during both stress periods after two minutes (8% below baseline). When cold immersion was prolonged for three minutes the ejection fraction remained significantly depressed until the end of the stress period. Figure 6 shows the ejection fraction response to two minutes and three minutes of isometric hand grip. Two minutes' exertion at 50% maximum voluntary contraction induced a maximum fall in ejection fraction of 12% after 90 seconds with recovery at two minutes. Three minutes of isometric hand grip at 33% maximum voluntary contraction induced a fall of 7% at 90 seconds which then remained depressed until the end of exercise.

There were no statistically significant differences between the falls in ejection fraction during two minutes and three minutes of cold stress or two minutes and three minutes of isometric exercise; however, the number of subjects may have been too small to establish such a difference.

Nine subjects underwent repeat testing two weeks later (range 1–4 weeks). The standard error of the change in ejection fraction on the two separate occasions was 5·4% at rest, 4·8% for cold stress, and 7·0% for isometric exercise.

## Discussion

Early studies of isometric exercise suggested that measurement of the haemodynamic response to this form of exertion may provide a useful index of myo-

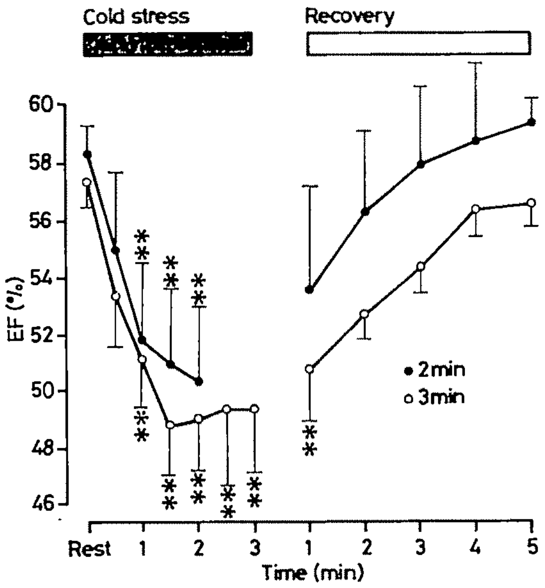

Fig. 5 *Mean (SE) left ventricular ejection fraction during two minutes' and three minutes' cold stress (n = 5).*
*$^{**}p<0{\cdot}01$ when compared with values at rest.*

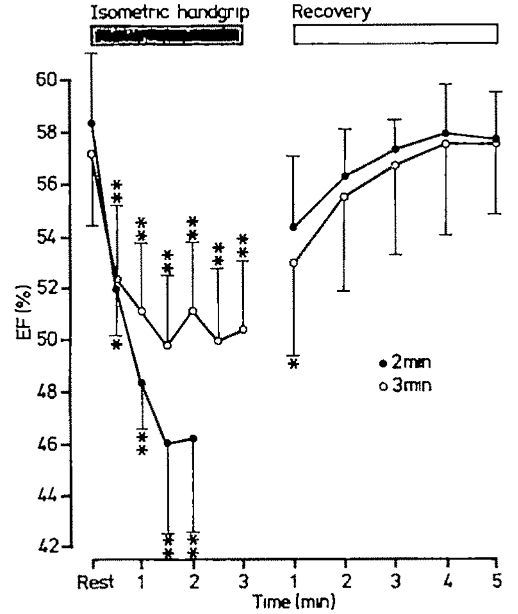

Fig. 6 *Mean (SE) left ventricular ejection fraction during two minutes' isometric hand grip at 50% maximum voluntary capacity and three minutes' isometric hand grip at 33% maximum voluntary capacity (n=5) *p<0·05; **p<0·01 when compared with values at rest.*

cardial dysfunction.[2] Helfant *et al*, however, found isometric exercise to be of no value for the detection of coronary artery disease and suggested that the increase in diastolic blood pressure that occurs during the test may prevent the development of myocardial ischaemia.[11] Using radionuclide techniques, Bodenheimer *et al* suggested that the assessment of regional ejection fraction during isometric hand grip may also be of value,[12] but more recently the same group of workers found a specificity of only 50% for the detection of coronary artery disease when considering global ejection fraction.[5] During cold stress, Wainwright *et al* reported a clear separation in the response of left ventricular ejection fraction between normal subjects and patients with coronary artery disease or cardiomyopathy,[13] whereas Jordan *et al* and Wasserman *et al* were unable to detect a clinically important difference between normal and diseased subjects.[6,7] In one of these studies, the fall in left ventricular ejection fraction in response to cold was slightly more pronounced in normal subjects than in patients with coronary artery disease.[6] Using techniques similar to our own, Giles *et al* found a mean fall of 11% in both patients and controls in response to cold stress and isometric hand grip.[14] These studies were limited to the investigation of ejection fraction, however, and little attention has been paid to changes in relative volumes.

Several factors may be responsible for this wide variation in reported results. These include differing selection criteria for both patients and normal controls. In previously reported studies normal controls were patients who had undergone coronary arteriography for investigation of chest pain, with negative results.[7,13] This group of patients has been shown to have a highly variable response when the ejection fraction during dynamic exercise is studied.[15] It is debatable therefore whether they should be considered as truly normal, particularly when their response to cold stress is measured.

Protocols for isometric hand grip have ranged from two minutes exertion at 50% maximum voluntary contraction to three or four minutes at 30% maximum voluntary contraction,[12,16] and for cold stress from two to five minutes of hand immersion.[6,7] In all these studies different radionuclide techniques have also been used including gated radionuclide angiography with a data acquisition time of two to five minutes[6] and first pass radionuclide angiography with both $^{99m}$Tc[16] and $^{195m}$Au.[17]

The nuclear stethoscope has been fully validated for the measurement of resting left ventricular ejection fraction.[8,9] In a recent study of 54 patients we compared the resting left ventricular ejection fraction measurements from the nuclear probe with those from a gamma camera.[18,19] The mean (SE) difference between the two methods was 1·4(0·8)%, confirming the validity of the nuclear probe. It is reasonable to expect this accuracy to apply during isometric hand grip and cold stress, which involve no additional patient movement. One important source of error during these interventions might be expected from significant changes in background activity. We are able, however, to reassess background counts during each stress test and make any necessary corrections. Using a positron camera, Nichols *et al* have shown that cardiopulmonary blood volume increases in patients with coronary artery disease during exercise testing.[20] The background counts in our normal population may not, however, be appropriate when applied to patients.

The overall fall in ejection fraction of 4·5% obtained by gated measurement at the peak of cold stress is in the middle of the range of other reported studies in "normal" subjects (+3% to −11%).[4,11,21] Only three of our subjects increased their ejection fraction during cold stress and in seven a fall of >4·8% developed. The maximum fall occurred after one minute, in keeping with the results obtained by Dymond *et al.*[17] When the cold stress test was prolonged for three minutes, the ejection fraction remained depressed for the period of the intervention and the recovery was again slow. These results are in contrast with those obtained by Manyari *et al* who demonstrated an abnormal ejection fraction response in only two out of 20 "normal" subjects.[21]

The mean fall in left ventricular ejection fraction of 9·3% in response to 50% maximum voluntary contraction during isometric hand grip contrasts with one earlier study reporting a rise of 3%, but compares well with more recent studies reporting a 7–12% fall.[5 11] Fifteen of our subjects decreased their ejection fraction by more than 7% and only two subjects demonstrated an increase in ejection fraction at peak intervention. The maximal fall during 50% maximum voluntary contraction occurred after 90 seconds with a slight recovery at two minutes. This is probably related to the fact that subjects found it difficult to maintain this degree of contraction, and some relaxation of grip occurred. During three minutes of hand grip at 33% maximum voluntary contraction left ventricular ejection fraction was less severely affected, but remained depressed for the duration of the stress. It was apparent that the subjects were better able to maintain this degree of grip.

Our measurements of resting left ventricular ejection fraction made with the nuclear probe on two occasions showed a standard error that resembles those reported in other studies in which the non-imaging nuclear probe[9 10] and gamma cameras[22–24] were used. The standard error of the ejection fraction at the peak of cold stress was similar but the response to isometric hand grip was less reproducible.

The findings in this study are not surprising in the light of the sequence of physiological events. Both these stress tests lead to an increase in aortic diastolic pressure. The normal left ventricle must first overcome this pressure during the isovolumetric phase of contraction before blood is ejected. As the aortic pressure begins to rise, the volume of blood ejected from the left ventricle will be reduced for the first few beats. If the aortic diastolic pressure were then maintained at a constant level the ventricle would restore the initial ejection fraction by the Frank-Starling mechanism. As the systemic diastolic pressure continues to rise, a progressive fall in ejection fraction occurs until the point at which blood pressure decreases. This sequence of events is important in determining the left ventricular response, irrespective of the presence or absence of coronary artery disease.

There was considerable inter-subject variability in response to both of these stress tests. There was only moderate agreement between repeat measurements under stress conditions in any individual although for the group as a whole the reproducibility was good. This intra-subject variability may in part have reflected the methods we used, although neither of these interventions provoked any additional patient movement, particularly of the chest wall. Our results suggest that the maximum fall in left ventricular ejection fraction does not necessarily occur at the peak of the stress and therefore techniques requiring data acquisition times of two to five minutes may, as a result of the inherent averaging which occurs, underestimate the induced changes.

In conclusion therefore, it appears that a combination of inter-subject variability and considerable methodological differences have contributed to the reported discrepancies between published reports. These factors, as well as the physiological responses to these stress tests, are likely to limit severely the usefulness of these tests for the detection of coronary artery disease, particularly in an unselected population.

We thank Mr D Hinge, Mr J Tovey, and Dr Heather Prince for their technical help and Mr John C W Crawley for his advice.

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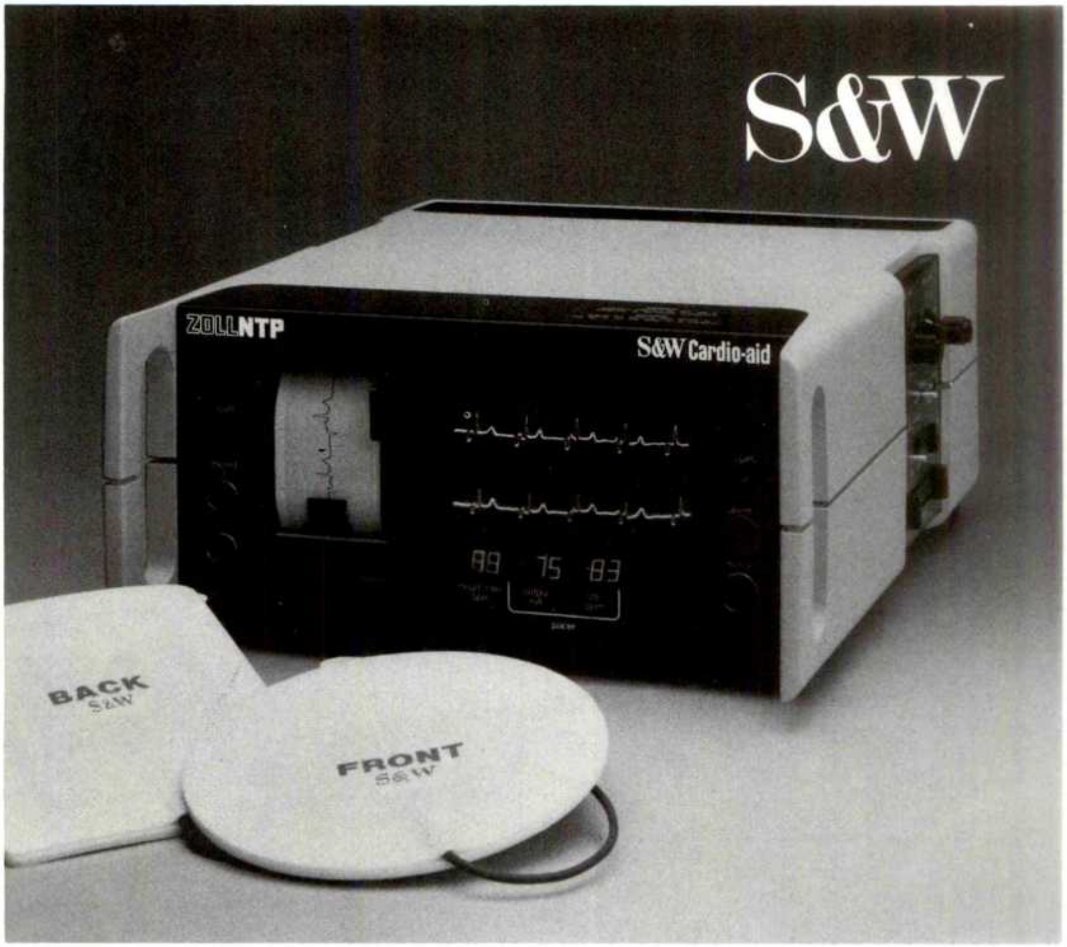

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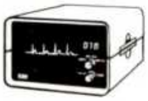
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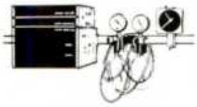
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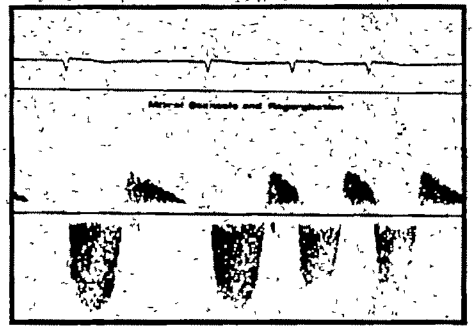

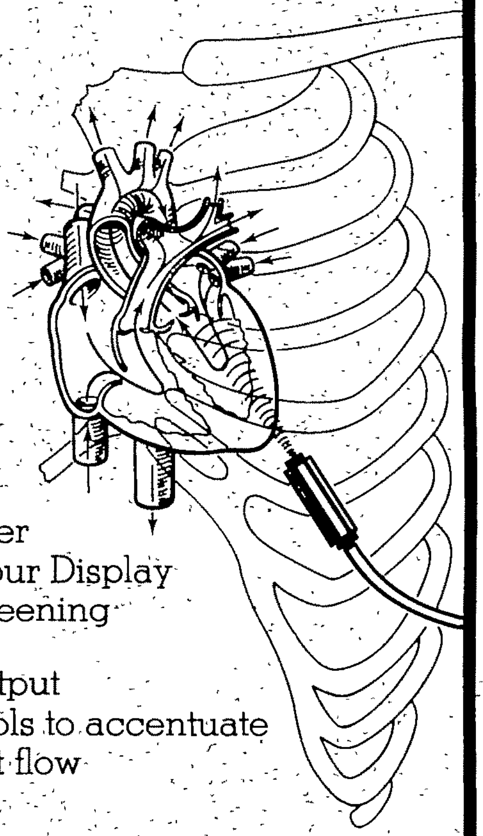

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# Diurnal variation of the QT interval—influence of the autonomic nervous system

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SUMMARY To assess the influence of diurnal changes in the autonomic nervous system on the QT interval, 24 hour dynamic electrocardiographic monitoring was performed in six pacemaker dependent patients with normally innervated hearts, in six cardiac transplant patients with anatomically denervated hearts (but which respond to circulating catecholamines), and in nine diabetic patients with confirmed autonomic neuropathy. QT and RR intervals from hourly intervals were measured and Bazett's formula was used to correct QT intervals during sinus rhythm. All QT intervals were normalised by dividing by the mean QT for the 24 hours in each patient and were expressed as a percentage. There was pronounced diurnal variation of normalised QT in the patients with normally innervated hearts. QT intervals were longer during sleep than during waking hours (06.00 *vs* 18.00 h, 102·5% *vs* 97·8%). Diurnal variation was blunted in the transplant patients (101·3% *vs* 98·1%) and absent in the diabetic patients (100·0% *vs* 100·3%). In the normally innervated patients changes were most pronounced at the time of waking (06.00 *vs* 09.00 h, 102·5% *vs* 95·4%). There was no change in normalised QT in the transplant and diabetic patients at this time. There was no significant difference between normalised QT for the three groups during sleep, but this variable was shorter in innervated patients during waking hours (for example at 10.00 h, innervated 96·5%, transplant 100·7%, diabetic 100·7%). Diurnal changes of the QT interval may be pronounced in the innervated heart and are dependent on both variations in autonomic tone and concentrations of circulating catecholamines. These changes in repolarisation may be related to the reported diurnal pattern of ventricular arrhythmias.

The QT interval on the surface electrocardiogram is an indirect measure of myocardial depolarisation and repolarisation. Abnormalities of the QT interval, which indicate abnormal repolarisation, have been linked with the development of ventricular arrhythmias, principally in the long QT syndromes[1-3] and after myocardial infarction.[4 5] Recently there has been considerable interest in the dynamic nature of the QT interval, both normal and pathological,[6] and in particular it has been suggested that the QT interval may be increased during sleep independently of any changes in heart rate.[7] The possible mechanism of this lengthening remains speculative.

There are pronounced changes in autonomic balance during sleep, with either an increase in parasympathetic tone or a decrease in sympathetic activity or both, depending on the phase of sleep.[8] There is also a diurnal variation in circulating endogenous catecholamines—catecholamine output is lower during the night.[9 10] All of these factors could influence myocardial repolarisation, and thus the QT interval, independently of any changes in heart rate that they may produce.

We have attempted to ascertain whether there is diurnal variation of the QT interval, and by using groups of patients with varying degrees of cardiac denervation to gain insight into the possible autonomic mechanisms involved.

## Patients and methods

### PATIENTS

Three groups of patients were investigated.

*Group A* consisted of six patients with permanent

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Accepted for publication 4 November 1985

implanted constant rate ventricular demand pacemakers. Their ages ranged from 62 to 84 (mean 73) years and four were men. All patients were totally pacemaker dependent with no sinus or fusion beats during any electrocardiographic recording. These are patients with normally innervated hearts which respond both to changes in neurally mediated autonomic tone and to circulating catecholamines.

*Group B* consisted of six orthotopic cardiac transplant recipients. Their ages ranged from 25 to 50 (mean 37) years and all six were men. They were studied 4 to 18 (mean 13) months after operation and at the time of this investigation all patients were completely symptom free with no haematological, biochemical, or electrocardiographic evidence of rejection. All patients were taking prednisolone and azathioprine as routine immunosuppressive treatment. Within 48 hours of the ambulatory monitoring reported below, the patients had undergone electrophysiological evaluation during which various physiological manoeuvres, including carotid sinus massage, the cold pressor test, and the Valsalva manoeuvre had been performed.[11] In no case was there a change in either donor heart rate or any conduction interval, confirming the persistence of functional cardiac denervation. Thus these are patients with anatomically denervated hearts which respond solely to circulating catecholamines.

*Group C* consisted of nine insulin dependent diabetic patients. Their ages ranged from 32 to 61 (mean 43) years and seven were men. All had two or more of the following symptoms suggestive of autonomic neuropathy—impotence, postural hypotension, diarrhoea, perspiration problems, hypoglycaemia unawareness, and gastric stasis symptoms and all had abnormal cardiovascular reflexes indicating both cardiac parasympathetic and more widespread sympathetic damage. Heart rate response to the Valsalva manoeuvre, to deep breathing, and to standing (for parasympathetic damage) and the blood pressure response to standing and to sustained handgrip (for sympathetic damage) were tested.[12]

All patients in the three groups met the following criteria: *(a)* they were not on medications known to influence the QT interval, *(b)* they had no or very infrequent atrial or ventricular premature beats, and *(c)* in those patients in sinus rhythm (groups B and C), there was no evidence of bundle branch block. Apart from one diabetic patient with known coronary artery disease, no other patient in the three groups had important confirmed ischaemic or structural heart disease.

### METHODS

All patients underwent at least 24 hours of continuous ambulatory electrocardiographic monitoring on either four inch reel to reel two channel tape recorders or two channel cassette recorders (groups A and B) or single channel cassette recorders (group C). No attempt was made to control the patient's activities during the 24 hours of monitoring; however, all patients had a conventional daily activity pattern—that is they slept at night and were active during the day. Tracings of approximately 10 QRS complexes were printed out every hour for each patient. The RR and QT intervals for each hour were measured blindly and in random order by two observers, who were unaware of the patient's name and the hour of the day but not, because of the differing recording equipment used and the presence of paced beats, the group. Each observer averaged the results of two or three complexes, and then the results of the two observers were averaged. The QT interval was measured from the beginning of the Q wave to the point at which the T wave returned to the isoelectric line. QT intervals during sinus rhythm were corrected for heart rate by means of Bazett's correction ($QTc = QT/RR^{0\cdot5}$, with the RR interval expressed in seconds).[13] To overcome any bias engendered by the longer measured QT intervals of the ventricular paced complexes (that is because a similar percentage change would produce a greater absolute change), all QT intervals were normalised by dividing by the mean QT interval for the 24 hours in each patient and were expressed as a percentage.

### STATISTICAL ANALYSIS

All values are quoted as the means and one standard deviation. We compared data by Student's two tailed *t* test for paired and non-paired data. Differences of $p<0{\cdot}05$ were regarded as significant.

## Results

*Group A*—All patients had multiprogrammable ventricular pacemakers (Medtronic 5985) which were programmed to the same pacing rate (70 beats per minute) at the time of this study. There was a pronounced diurnal variation in the normalised QT interval over the 24 hours, with significantly longer QT intervals during sleep than during waking hours (see Table and Fig. 1) (for example 06.00 h *vs* 18.00 h, $p<0{\cdot}01$; 05.00 h *vs* 17.00 h, $p<0{\cdot}01$). The QT interval tended to lengthen during the hours of sleep with the longest intervals being recorded at 05.00 h. The biggest changes occurred at the time of wakening. The QT interval shortened from 103·4% at 05.00 h to 95·4% at 09.00 h ($p<0{\cdot}001$). The mean measured QT interval for this group was 461 ms, and this shortening therefore represents, in absolute

Table *Normalised QT intervals for the three groups over the 24 hour period*

| *Time (h)* | *Group A (V paced)* | *Group B (transplants)* | *Group C (diabetics)* |
|---|---|---|---|
| 13.00 | 95·0 | 99·8 | 98·7 |
| 14.00 | 95·0 | 98·1 | 99·9 |
| 15.00 | 95·7 | 99·2 | 100·4 |
| 16.00 | 96·8 | 98·9 | 99·7 |
| 17.00 | 98·1 | 98·5 | 99·8 |
| 18.00 | 97·8 | 98·1 | 100·3 |
| 19.00 | 98·7 | 98·1 | 100·0 |
| 20.00 | 100·0 | 98·3 | 100·9 |
| 21.00 | 97·8 | 97·1 | 99·5 |
| 22.00 | 97·9 | 99·3 | 100·6 |
| 23.00 | 100·0 | 98·5 | 99·5 |
| 24.00 | 101·9 | 100·5 | 100·4 |
| 01.00 | 101·2 | 101·3 | 99·6 |
| 02.00 | 101·2 | 101·4 | 100·2 |
| 03.00 | 101·1 | 101·2 | 99·9 |
| 04.00 | 102·3 | 100·6 | 100·1 |
| 05.00 | 103·4 | 101·5 | 100·5 |
| (05.30) | (103·0) | — | — |
| 06.00 | 102·5 | 101·3 | 100·0 |
| (06.30) | (101·3) | — | — |
| 07.00 | 101·2 | 102·4 | 99·7 |
| (07.30) | (99·1) | — | — |
| 08.00 | 95·9 | 100·6 | 99·4 |
| 09.00 | 95·4 | 102·2 | 100·3 |
| 10.00 | 96·5 | 100·7 | 100·7 |
| 11.00 | 95·4 | 101·9 | 98·4 |
| 12.00 | 95·7 | 100·5 | 100·3 |

All values are in percentages V, ventricular.

terms, a change of 37 ms in the measured QT. The shortening was maintained during the active hours of the day and then the QT interval gradually lengthened during the evening. The average difference between definite sleeping hours (01.00–06.00 h) and definite waking hours (10.00–22.00 h) was 5·0% or 23 ms in absolute terms. Having analysed the data as indicated in the methods section, we retrospectively analysed the intervening 30 minute intervals at the time of the most rapid change and these are included in the Table in parentheses.

*Group B*—There was little variation in mean hourly heart rate over the 24 hours in group B patients—the maximum to minimum heart rate difference being 17·2 beats per minute (Fig. 2). The greatest difference in maximum and minimum heart rate in any one of the patients was 29 beats per minute. Diurnal variation of the QT interval was present but was considerably blunted with only slightly longer QT intervals during sleep than during waking hours (Table and Fig. 1). At no time did the difference between a sleeping hour and a waking hour achieve statistical significance. In contrast with the normally innervated patients (group A) there was no change in the QT interval at the time of waking. The average difference between definite sleeping and waking hours was 2·1% (in absolute terms 9 ms).

*Group C*—As with group B patients there was little variation in mean hourly heart rate, maximum to minimum heart rate difference being 17·5 beats per minute (Fig. 2). The greatest difference in maximum and minimum heart rate in any one patient was 37 beats per minute. Diurnal variation of the QT interval was completely absent with no difference between sleeping and waking hours (Table and Fig. 1). The average difference between definite sleeping and waking hours was 0·11% (in absolute terms 0·5 ms).

Figure 1 shows that there are no significant differences in normalised QT interval among the three groups during the hours of sleep, although there was some lengthening in the innervated patients before waking. The QT interval, however,

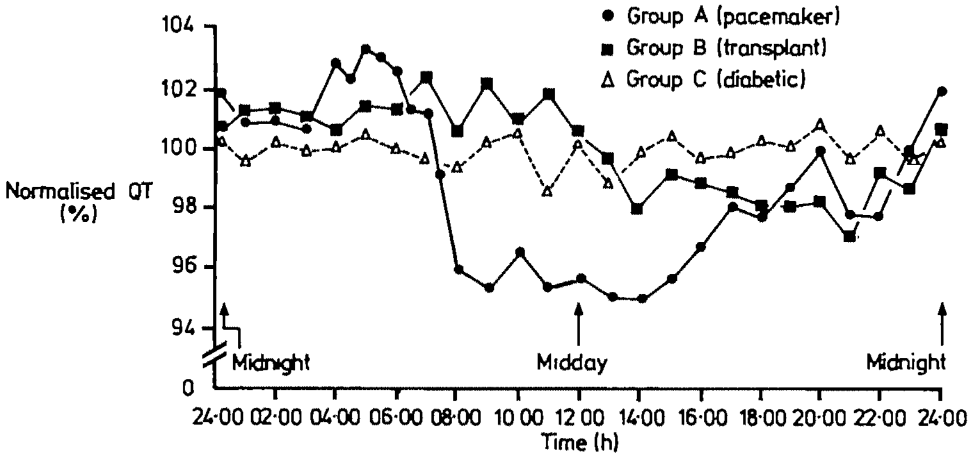

Fig. 1 *Normalised QT interval plotted against absolute time of day for group A (paced patients), group B (transplant patients), and group C (diabetic patients).*

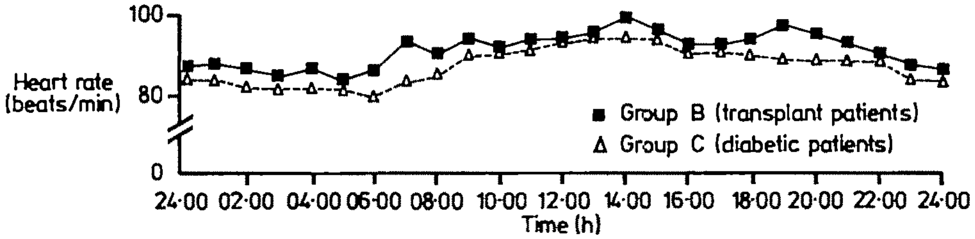

Fig. 2 *Mean hourly heart rate plotted against absolute time of day for transplant patients and diabetic patients.*

was significantly shorter during waking hours in those with innervated hearts (for example at 10.00 h group A, 96·5%; group B, 100·7%; group C, 100·7% ($p < 0·01$)). The interobserver differences in measured QT were small—for example for all measurements in group A patients the differences ranged from 0 to 20 (mean 2·3 ms).

## Discussion

These data confirm the previous work of Browne *et al* indicating that the QT interval is prolonged during sleep.[7] The methods and patient groups that we studied meant that we were able to gain some insight into the possible physiological mechanisms. Browne *et al* suggested that this prolongation may reflect either increased vagal tone or sympathetic withdrawal, in other words a net increase in parasympathetic tone. They made no mention of the possible role of circulating catecholamines, which are known to influence the QT interval.[14] Also because they compared RR intervals of identical duration during wakefulness and sleep, they were not able to comment on the possible time course of events.

When the effect of an intervention on the QT interval is assessed it is usual to correct for changes in heart rate.[13 15] When there is a considerable change in heart rate, however, the application of a correction factor such as Bazett's formula may lead to spurious and misleading results.[16–18] Bazett's formula may only be accurate when the heart rate is between 50 and 115 beats per minute,[16] and more recently some workers have suggested an even smaller range of rates (RR intervals, 700 ms to 1050 ms).[7] To circumvent this problem Milne *et al* suggested that the effects of an intervention on the QT interval should be assessed at identical atrial[17] or ventricular[19] paced rates. In this study we assessed patients at ventricular paced rates. It could be argued that the absence of changes in the transplant and diabetic patients is related to errors engendered by the use of Bazett's correction in these groups. Figure 2, however, shows that the variation in heart rate in these two groups is extremely small and within the range over which Bazett's correction is probably valid.

For a long time it has been accepted that the heart rate slows during sleep and that this is related to considerable diurnal changes in the autonomic nervous system.[20 21] It was initially felt that this fall in heart rate during sleep was entirely related to an increase in parasympathetic tone.[20] Samaan in 1934, however, suggested that there was an additional decrease in sympathetic activity.[22] More recent work, in which different kinds and degrees of heart denervation were studied, has also indicated that both an increase in vagal tone and decreased sympathetic discharge occur, depending on the phase of sleep.[8] After complete cardiac denervation by combined bilateral vagotomy and stellectomy the decrease in heart rate during sleep, although markedly reduced, still occurred.[8] There is also a circadian variation in concentrations of circulating endogenous catecholamines.[10] In the study by Barnes *et al*, the highest values of plasma adrenaline were recorded at 16.00 h and the lowest values at 04.00 h.[10]

All of these autonomic factors, as well as affecting heart rate, have been shown to influence the QT interval independent of any changes in rate. Assessment of the QT interval by the pacing technique mentioned previously has shown that loss of parasympathetic tone induced by atropine shortens the QT interval[13 23] and ventricular effective refractory period[24] and that loss of sympathetic tone induced by propranolol either has no effect[18 23] or may tend to prolong[17] the QT interval and ventricular refractory periods.[24] Thus both the increase in parasympathetic tone and decrease in sympathetic activity occurring during sleep[8] will tend to lengthen the QT interval independently of the slowing in heart rate. Similarly the infusion of catecholamines has been shown to shorten the QT interval, again independently of rate changes,[14] suggesting that the low concentrations encountered during sleep will lead to a relative lengthening of this interval.

Thus the autonomic changes occurring during sleep will all tend to lengthen the QT interval. That this actually occurs is illustrated by the normally innervated patients in group A who had significantly longer QT intervals during sleep than during waking hours. The QT interval tended to lengthen during the hours of sleep, with the longest intervals being seen at 05.00 h when the concentration of circulating catecholamines is at its lowest[10] and when previous studies have documented that the heart rate is slowest.[21 25] The QT interval shortened rapidly during the hours of waking, during which plasma adrenaline concentrations are rapidly rising,[10] and there is inhibition of the parasympathetic cardioinhibitory centre at the time of arousal.[8] Obviously other factors such as physical exertion and meals may have influenced the QT interval during waking hours but these activities probably only account for a minor portion of the data collected for each patient and are presumably similar in the three groups.

Diurnal variation of the QT interval was still apparent in the transplant patients, with longer QT intervals during sleep, although the changes were not significant and were considerably blunted compared with those in the innervated group. The transplanted heart seems to remain functionally and anatomically denervated indefinitely,[26 27] although it responds appropriately to catecholamines.[28] Thus any changes observed in the QT interval, corrected for heart rate, must be related to changes in the concentration of circulating catecholamines. Although the QT interval in this group tended to lengthen towards the end of sleep, it is interesting that the longest QT interval was delayed by approximately two hours compared with that in innervated patients and did not coincide with the time at which circulating catecholamines might be expected to be at their lowest concentration.[10] The reason for this apparent discrepancy is unclear.

In the diabetic patients, who had proven autonomic neuropathy, there was no diurnal variation of the QT interval. These patients with advanced, symptomatic cardiac parasympathetic and more widespread sympathetic damage do not respond to neurally mediated changes in autonomic tone.[12] It has also been shown that plasma catecholamine concentration is reduced in long term diabetics with signs of somatic neuropathy and indeed that there is a close correlation between this reduction in plasma catecholamine concentration and the degree of autonomic neuropathy,[29] which was quite severe in the group C patients. Long term diabetic patients may also show an abnormally blunted plasma catecholamines response to manoeuvres such as standing.[29] Unfortunately data on the diurnal variation of catecholamines in diabetics with proven neuropathy are not available.

It is apparent from these data that there is diurnal variation of the QT interval in the normally innervated heart which may be quite pronounced. This variation appears to be dependent, perhaps to an equal extent, on changes in both neurally mediated autonomic tone (presumably predominantly heightened parasympathetic tone during sleep) and on the circadian variation in circulating catecholamines. Several studies have shown that sleep is associated with a decrease in both the frequency and severity of ventricular arrhythmias both in patients with ischaemic heart disease and in healthy subjects.[30-32] It is therefore interesting to note that in the innervated patients (group A) the longest QT intervals, at a constant heart rate, occurred at the same stage of sleep that previous studies have documented the lowest frequency of arrhythmias.[32] It is tempting to suggest that those autonomic factors which lengthen the QT interval may, independently of any effect they may have on heart rate, reduce the temporal dispersion of refractoriness and thus the tendency for arrhythmias.

We thank Dr David Ewing, The Royal Infirmary, Edinburgh for providing the 24 hour tapes on the diabetic patients.

A J C is Sir Ronald Bodley Scott Professor of Cardiovascular Medicine (supported by the British Heart Foundation).

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# Frequency of extrasystoles in healthy male employees

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SUMMARY To determine reference values for ectopic activity 147 actively employed healthy men aged from 15 to 65 years were examined by 24 hour Holter monitoring during their ordinary daily activities. Age was the only risk factor significantly associated with supraventricular and ventricular extrasystoles. During a six year follow up only two men died. In both the frequency of ventricular extrasystoles had been high, but neither of them died from cardiovascular disease.

Because the distribution of the frequency of extrasystoles in the study group was highly skewed a percentile distribution was used to determine normal values. This distribution showed that 95% of men aged 15–39 years had <2·9 ventricular extrasystoles per hour and the same proportion of men aged 40 years or older had <36 ventricular extrasystoles per hour. For field studies values above the 90th percentile (that is more than 10 ventricular extrasystoles per hour for men 40 years or older) may be a more appropriate cut off point.

Ambulatory electrocardiographic monitoring of cardiac arrhythmias is commonly used in the clinical evaluation and prognostic assessment of ischaemic heart disease.[1 2] The importance of recording cardiac arrhythmia, in particular ventricular extrasystoles has been established by several studies.[3–5] Reliable population reference values are needed. We have measured the frequency of ectopic activity, both ventricular and supraventricular, in a healthy screened sample of working men aged 15 to 65 during their regular daily activities. Their work varied from unskilled labour to administrative managerial posts. The aim of the study was to establish criteria for normal values of ectopic activity in a male working population and to assess the prognostic importance of such ectopic activity.

## Subjects and methods

160 working men aged 15–66 years were selected from the payrolls of four large Swedish companies. Seventy three per cent were blue collar workers and 27% were white collar workers. They were included in the study if they were free from clinical signs of heart disease and other chronic disorders such as treated hypertension, diabetes, or hypercholesterolaemia and had a normal standard resting electrocardiogram. Thirteen men were excluded because they were on regular medication. Table 1 summarises the mean values and standard deviations of clinical variables.

A 24 hour ambulatory electrocardiogram was recorded with an Avionics Cardiocorder Model 400 in the normal work and home setting of each man. He recorded his activities for each of the 24 hours in a diary. The tapes were analysed by means of Avionics Composite Electrocardioscanners Model 650 after scanning with Reynolds Pathfinder Highspeed ECG Analysers. All suspected abnormalities were printed on electrocardiographic paper and reviewed by an independent cardiologist according to standardised procedures.[1]

Mean heart rates were calculated and the numbers of supraventricular and ventricular extrasystoles were counted per hour. The criteria for classification of ventricular ectopic beats were the following: absence of P wave; QRS configuration different from the regular complex; QRS width >0 12 s; prematurity and compensatory pause. Extrasystoles that did not meet these criteria were classified as supraventricular.

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Accepted for publication 11 November 1985

Table 1 *Clinical characteristics of the study group*

| *Characteristic* | *Mean (SD)* | *Range* |
|---|---|---|
| Age (yr) | 44·1 (14·1) | 15–66 |
| Systolic blood pressure (mm Hg) | 132·0 (14·9) | 105–188 |
| Diastolic blood pressure (mm Hg) | 79·4 (10·1) | 50–115 |
| Serum cholesterol (mmol/l) | 5·9 (0·9) | 3·8–8·6 |
| Alcohol consumption (kg absolute alcohol/year) | 3·2 (3·6) | 0·0–16·0 |
| Relative weight (weight (kg)/height (cm) −100) | 0·99 (0·13) | 0·73–1·45 |
| Proportion smokers | 47% | Occasional to >25 cigarettes per day |
| Proportion ex-smokers | 24% | |

All men were followed for six years, during which time deaths were recorded. The number of expected deaths was calculated by computing 5 year age group, calendar year, and gender specific person-years and multiplying these by the national death rates in 1978–83 and summing up the fractional contributions.[6]

STATISTICAL METHODS

Because of the skewed distribution of the frequency of extrasystoles in healthy subjects, non-parametric tests were generally used for statistical analyses. Thus, $\chi^2$ analyses were applied to test the association between frequency of extrasystoles and different risk factors including age. We used analysis of variance test with repeated measurements to assess the change in frequency of extrasystoles and of heart rate during different types of activity. In this case attempts were made to reduce the skewness of the investigated distributions by the use of medians and of logarithmic transformations.

## Results

For each individual the average number of extrasystoles per hour was calculated as the total number of extrasystoles divided by the number of recorded hours. Table 2 shows the results for different age groups. Because of the skewed distributions of the variables that we investigated the results are shown for subgroups defined by the increasing magnitude of the ectopic activity. The lowest group consists of those individuals who had no ectopic beats. The group limits were chosen primarily to conform with earlier studies, but also to show the distribution, which includes some very high values. Supraventricular extrasystoles were found in three-quarters and ventricular extrasystoles in almost half of the men; most of these cases were in the group with up to one extrasystole per hour.

The number of extrasystoles per hour increased significantly with age (Table 2). Except for one man, men aged <45 years did not have as many as 20 ventricular extrasystoles per hour. Five out of 46 men over age 55 had an average of more than 20 supraventricular extrasystoles per hour during the study period.

The Figure shows the diurnal variation of mean heart rate and of median frequency of ventricular extrasystoles. An analysis of variance test showed that mean heart rate ($p<0·001$), mean log frequency of ventricular extrasystoles ($p<0·01$), and mean log frequency of supraventricular extrasystoles ($p<0·05$) were significantly higher during working hours than during sleep. Because of the pronounced skewness of the distribution of ectopic beats in these healthy men it was not possible to calculate an equation that predicts the number of ventricular or supraventricular extrasystoles expected at a given age. Instead we give the age-adjusted expected number of extrasystoles in the 90th and 95th percentile (Table 3).

Thus in 90% of men under age 40 one would expect to find only occasional extrasystoles, that is less than one supraventricular or one ventricular extrasystole per hour. In 90% of men of 40 years or older, still quite modest numbers of extrasystoles are expected (6·5 supraventricular and 9·7 ventricular per hour). Five per cent of healthy men, however, do have extreme values—for example some men of 40 years or older have 19·2 supraventricular and 36 ventricular extrasystoles per hour.

Complex ventricular arrhythmia was rare, even in older men (Table 4). Only two of 70 men under age 45 had coupled or multiform ventricular extrasystoles. The R on T phenomenon was found in one man and a run of ventricular tachycardia in another; both were more than 45 years old.

We also analysed the association between the frequency of extrasystoles and clinical variables. There was no statistically significant increase in the frequency of supraventricular or ventricular extrasystoles in men with raised systolic or diastolic blood pressure, raised serum cholesterol, in those who were smokers, or in those who were overweight (Table 5). The frequency of supraventricular extrasystoles but not that of ventricular extrasystoles was significantly higher in men who reported drinking

Table 2 *Proportions of men in different age groups showing ventricular and supraventricular extrasystoles. Percentages are given in parentheses*

| *Extrasystoles* | *15–24 yr (n=17)* | *25–34 yr (n=26)* | *35–44 yr (n=27)* | *45–54 yr (n=31)* | *55–66 yr (n=46)* | *Total (n=147)* |
|---|---|---|---|---|---|---|
| Supraventricular | | | | | | |
| 0 | 6 (35) | 11 (42) | 10 (37) | 7 (23) | 3 (7) | 37 (25) |
| 0·1–0·9 | 9 (53) | 15 (57) | 15 (55) | 19 (61) | 16 (35) | 74 (50) |
| 1·0–4·9 | 0 | 0 | 0 | 4 (13) | 15 (33) | 19 (13) |
| 5·0–19·9 | 0 | 0 | 0 | 1 (3) | 7 (15) | 8 (5) |
| 20– | 2 (12) | 0 | 2 (7) | 0 | 5 (11) | 9 (6) |
| $\chi^2=48·6$ | df=8* | | | p<0·001 | | |
| Ventricular | | | | | | |
| 0 | 12 (70) | 20 (77) | 16 (59) | 15 (48) | 16 (35) | 79 (54) |
| 0·1–0·9 | 3 (18) | 5 (19) | 8 (30) | 12 (39) | 24 (52) | 52 (35) |
| 1·0–4·9 | 1 (6) | — | 2 (7) | — | — | 3 (3) |
| 5·0–19·9 | — | 1 (4) | 1 (4) | 1 (3) | 3 (7) | 6 (4) |
| 20– | 1 (6) | — | — | 3 (10) | 3 (7) | 7 (5) |
| $\chi^2=15·85$ | df=8 | | | p=0·045 | | |

*For a better approximation to the assumption of the $\chi^2$ test the three groups with highest frequencies were aggregated into one group Hence the df is 8 According to Armitage this approximation of the $\chi^2$ distribution is reasonable because relatively few expected frequencies are less than 5[24] If, however, we maintain the more orthodox view that none of the expected frequencies should be less than 5, the table would be aggregated into 0 and >0 categories In that case df is 4, and $\chi^2=15·6$, p=0·0036 for supraventricular extrasystoles and $\chi^2=14·9$, p=0·0049 for ventricular extrasystoles

more than 2000 g of alcohol per year which corresponds to approximately 40 g of ethanol per week (Table 5).

We also attempted to analyse the significance of extrasystoles in relation to six years mortality. Only two men died during the follow up period (one from respiratory insufficiency, one from Boeck's sarcoid). At necropsy neither had evidence of ischaemic heart disease or other cardiovascular disease. Based on the age distribution seven deaths would have been expected in the study group, 2·6 of them from ischaemic heart disease. Since treated risk factors for, and clinical and electrocardiographic signs of ischaemic heart disease had been used as exclusion criteria, the study group was made up of healthy employed men. This and the fact that employed men in general have a lower mortality than that of the average population explains the low death rate. Both men who died were over 60 years at the initial examination. Although they had only three and six supraventricular ectopic beats per hour respectively, they also had 227 and 39 ventricular ectopic beats per hour—that is more than the 95th percentile for men aged 40–66 years.

## Discussion

We have investigated the frequency of ectopic activity in healthy employed men. Only age was significantly associated with both ventricular and supraventricular ectopy. Most workers agree that ventricular arrhythmias become more common with

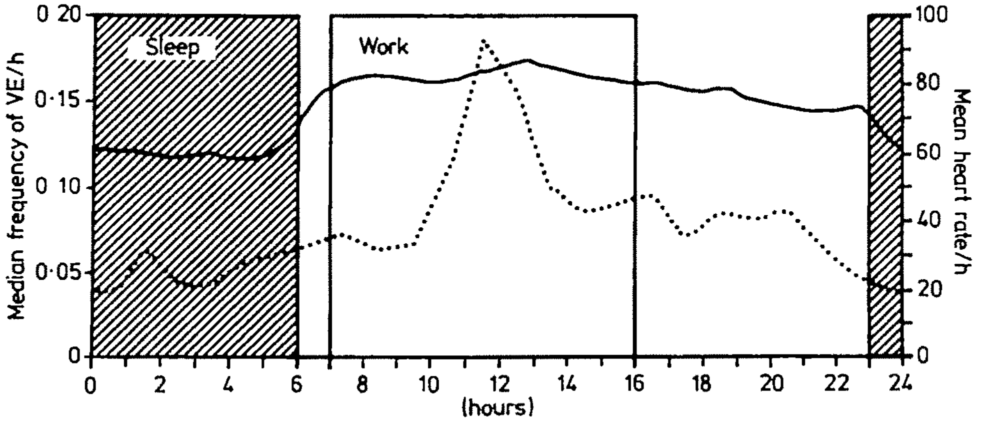

Figure *Diurnal variation of mean heart rate and of median frequency of ventricular extrasystoles per hour in 147 healthy working men*

Table 3 *Frequency of extrasystoles in healthy men for the 90th and 95th percentiles in the distribution of mean number of extrasystoles per hour*

| | *15–39 yr* | | *40–66 yr* | |
|---|---|---|---|---|
| | SVE/*h* | *VE/h* | *SVE/h* | *VE/h* |
| 90% | 0·6 | 0·4 | 6·5 | 9·7 |
| 95% | 21·0* | 2·9 | 19·2 | 36·0 |

SVE, supraventricular extrasystoles, VE, ventricular extrasystoles.
*This figure is an approximation based on linear interpolation.

age.[7–9] Brodsky *et al* and Sobotka *et al* found ventricular arrhythmias in 56% of young men and in 54% of young women.[10 11] Fleg and Kennedy found ventricular arrhythmias in 80% of elderly people (aged 60–85).[12] Taylor and Stout found considerably more ectopic activity in elderly subjects than young healthy ones,[13] but Dickinson and Scott found ventricular extrasystoles in as many as 41% of 100 monitored teenage boys.[14]

There is less agreement, however, about the absolute frequencies of ventricular extrasystoles in healthy men of various ages. Kostis *et al* recorded ventricular extrasystoles during 24 hours in patients who had undergone coronary angiography and who had less than 5–10% luminal obstruction of the coronary arteries.[15] Only 28% of 40–49 year old men had ventricular extrasystoles. Hinkle examined 301 middle aged, actively employed men and found ventricular extrasystoles in 62% of 10 hour recordings.[16] Clinical signs of heart disease were found in about one fifth of these men. The monitoring was carried out in a hospital-like setting. Manger Cats *et al* found ventricular extrasystoles in 71% of 40–49 year old healthy men who were monitored for 24 hours.[17] Bjerregaard examined 260 middle aged men and women for 24 hours and found ventricular extrasystoles in 57% of 40–49 years old subjects.[18] Romhilt *et al* found ventricular extrasystoles in 46% of 24 hour recordings in healthy women aged 40–49 years.[19] Except for the study by Kostis *et al* all the studies that we have mentioned used clinical examination, standard questionnaires, and resting electrocardiograms or other non-invasive techniques to select patients free from identifiable heart disease.

The explanation for the great divergence of reported results seems to be the differing criteria used to select healthy subjects. The more careful the examination procedure and the more rigorous the criteria for selection of a healthy group, the fewer the ventricular extrasystoles that are found. We monitored healthy subjects from a working population, after excluding subjects with risk factors. We wanted to describe a reference working population that would be an appropriate standard for use in general practice or in occupational health studies. This is the reason that we used easily applicable criteria for classification of ventricular extrasystoles. These include prematurity of and compensatory pause after the extrasystole; this will exclude occasional interpolated ventricular extrasystoles. In a careful re-examination of 50 of the 147 recordings we found only three interpolated ventricular extrasystoles out of a total of 3 134. This appears to be a negligible error in the recording of ventricular ectopic activity.

Table 4 *Numbers of men showing multiform (M) or coupled (C) ventricular extrasystoles*

| *Ventricular extrasystoles* | *15–24 yr (n=17)* | *25–34 yr (n=26)* | *35–44 yr (n=27)* | *45–54 yr (n=31)* | *55–66 yr (n=46)* | *Total (n=147)* |
|---|---|---|---|---|---|---|
| 0 | — | — | — | — | — | — |
| 0·1–0·9 | — | — | — | 2 (M), 1 (C) | 10 (M), 3 (C) | 13 (M), 4 (C) |
| 1·0–4·9 | — | — | 1 (M) | 1 (M) | 1 (M) | 2 (M) |
| 5·0–19·9 | — | — | — | 1 (M) | 1 (M), 2 (C) | 2 (M), 2 (C) |
| 20–166 | 1 (C) | — | — | — | 1 (C) | 2 (C) |

Table 5 *Associations between clinical characteristics and supraventricular and ventricular extrasystoles*

| *Clinical characteristics* | *SVE* | | | *VE* | | |
|---|---|---|---|---|---|---|
| | $\chi^2$ | *df* | *p* | $\chi^2$ | *df* | *p* |
| Systolic blood pressure ⩾160 mm Hg | 1·54 | 4 | 0·82 | 1·84 | 4 | 0·76 |
| Diastolic blood pressure ⩾90 mm Hg | 2·53 | 4 | 0·64 | 1·62 | 4 | 0·81 |
| Smoking | 6·48 | 4 | 0·17 | 1·83 | 4 | 0·77 |
| Alcohol consumption >2000 g/yr | 10·12 | 4 | 0·04 | 3·01 | 4 | 0·56 |
| Relative weight ⩾1·0 | 3·87 | 4 | 0·42 | 3·65 | 4 | 0·45 |
| Serum cholesterol mmol/l >(3·745+0·087 × age (yr)) | 3·02 | 4 | 0·56 | 6·08 | 4 | 0·19 |

SVE, supraventricular extrasystoles, VE, ventricular extrasystoles.

Our exclusion criteria reduced the range of coronary risk factor levels in the study group. This may in part explain the lack of association between risk factors and ventricular ectopic activity. The findings accord with those of another study, however, that showed no association between coronary risk factor levels and ectopic activity in healthy men.[20] In high risk groups, however, such associations have been shown.[21-23]

There were only two deaths in the six year follow up, and neither was from ischaemic heart disease. Although both men who died had many ventricular extrasystoles per hour they were also older; thus no inferences about the prognostic significance of frequent extrasystoles can be drawn. The low mortality that we found may merely reflect the exclusion of men with risk factors. Reports on the prognostic significance of ectopic activity in healthy individuals are inconclusive. Demonstration of an unfavourable prognosis in some studies may be the result of inclusion of a higher proportion of individuals with heart disease or risk factors for heart disease.[2 22 23] The calculation of an equation for the prediction of expected numbers of extrasystoles proved difficult. A multiple regression equation was computed of data derived from the logarithmic transformation of ventricular extrasystoles against values of clinical characteristics including age on the other. The point estimate for an individual with group means on clinical parameters was 1·85 ventricular extrasystoles per hour, but the 95% confidence intervals were approximately 0 10 to 26 0 ventricular extrasystoles per hour. This reflects both the skewed distribution of and great individual variability in the frequency of ventricular ectopy. The expected incidence of extrasystoles was also estimated from the 90th or 95th percentiles in different age groups. It was uncommon (1 in 20 men) to find more than 36 ventricular ectopic beats per hour in men aged >40 years. This finding warrants further clinical investigation.

We regard the 90th percentile value of >10 ventricular extrasystoles per hour in healthy men aged 40–66 years as indicating a high frequency on an ordinal scale. Because techniques and the methods for evaluation of ventricular ectopic activity are relatively constant this cut off point should be useful in comparative field studies.

We thank OHN Lena Janzon and secretary Margareta Gunnarsson at the Nitro Nobel Company. This study was sponsored by the Swedish Work Environment Fund, Örebro County Council, and the Seraphimer Hospital Foundation.

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# Vasodilatation with captopril and prazosin in chronic heart failure: double blind study at rest and on exercise

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SUMMARY A double blind cross over study was performed to compare the long term hormonal, haemodynamic, and clinical responses to specific inhibition of the renin-angiotensin-aldosterone system (captopril) and of the $\alpha_1$ adrenoceptors of the sympathetic system (prazosin) both at rest and during upright exercise in patients with chronic heart failure. Sixteen patients completed one month's treatment with each drug.

During conventional diuretic treatment (control) plasma renin activity, aldosterone, and noradrenaline were increased at rest and on exercise. Control left ventricular filling pressures were raised, and correlated significantly with plasma renin activity both at rest and on exercise. Systemic vascular resistance was increased at rest, and its reduction during exercise correlated inversely with the increase in plasma renin activity and plasma noradrenaline.

After one month's treatment with captopril there were reductions in plasma aldosterone, weight, left ventricular filling pressure, and systemic vascular resistance at rest and on exercise. Dyspnoea was relieved and exercise capacity increased. The greater fall in systemic vascular resistance on exercise no longer correlated with the increase in plasma renin activity. During treatment with prazosin there were increases in plasma noradrenaline and, transiently, in plasma aldosterone. Fluid retention occurred, and left ventricular filling pressure was unchanged. Compared with control values systemic vascular resistance was reduced at rest but not on exercise. Dyspnoea and exercise capacity did not improve.

In chronic heart failure, vasodilatation by inhibition of the $\alpha$ adrenergic system with prazosin causes compensatory stimulation of the renin-angiotensin-aldosterone system and does not result in clinical benefit. Inhibition of the renin-angiotensin-aldosterone system with captopril causes secondary vasodilatation at rest and on exercise and results in improvement in symptoms and exercise capacity.

The haemodynamic abnormalities that occur at rest and during exercise in chronic heart failure have been well documented[1 2] At rest ventricular filling pressures are usually raised, cardiac output is reduced, and there is arteriolar and venous constriction with abnormal distribution of blood flow. These abnormalities are accentuated during exercise and this results in breathlessness and fatigue. Treatment with directly acting vasodilating drugs usually produces acute haemodynamic changes, but the long term clinical response is often disappointing.

In chronic heart failure the sympathetic and renin-angiotensin-aldosterone systems are activated,[3 4] and this leads to vasoconstriction and fluid retention. Some studies have investigated the

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Accepted for publication 4 November 1985

importance of these neuroendocrine systems in heart failure in animals[5] and man[6-8] at rest, but there has been no controlled study of relations between hormonal changes, haemodynamic measurements, and clinical features on exercise during long term treatment of heart failure.

A double blind, randomised crossover trial was undertaken to compare the long term hormonal, haemodynamic, and clinical responses to specific inhibition of the renin-angiotensin-aldosterone system (with captopril) and of the $\alpha_1$ adrenoceptors of the sympathetic system (with prazosin) both at rest and during upright exercise in patients with chronic heart failure. The results of changes occurring at rest in this study have been reported elsewhere.[9]

## Patients and methods

We studied 16 patients (15 men) (mean age 62 years, range 48 to 74 years). All patients had been in heart failure for at least 3 months. The aetiology of heart failure was coronary artery disease without recent myocardial infarction in 10 patients and dilated cardiomyopathy in six. No patient had important valvar, hypertensive, or renal disease.

All patients were breathless on moderate exertion (New York Heart Association class II–III), with radiologically confirmed pulmonary venous hypertension and cardiomegaly (cardiothoracic ratio $>0{\cdot}5$), despite optimal diuretic treatment. Frusemide (mean daily dose 138 mg) was given in combination with amiloride (9 mg). Only the three patients in atrial fibrillation received digoxin for control of ventricular rate. Other vasodilating drugs and spironolactone were not used during the study. All patients gave written informed consent. The study was approved by the hospitals' ethical committees.

### STUDY DESIGN

Patients were observed during a one week control period, while they were on diuretics and placebo, to ensure that they were in a stable clinical state with constant body weight and without peripheral oedema.

Control haemodynamic and hormonal measurements were then made at rest and during treadmill exercise (see below). Patients were then randomly allocated to treatment and were started on captopril (25 mg eight hourly) or prazosin (2 mg eight hourly). These drugs were given double blind by the double dummy technique and the doses were doubled after one week. The doses chosen have been shown[7] to produce similar acute haemodynamic effects, and are often used in clinical practice.

After one month, clinical, haemodynamic, and hormonal measurements were repeated at rest and on exercise at least two hours after the morning medication. Each patient was then crossed over, without a washout period, to receive a month of treatment with the other drug, and measurements were repeated at the end of the second month.

The initial control dose of diuretics was maintained throughout the study, unless peripheral oedema developed with a weight gain of 2·5 kg or more, in which case the dose of frusemide was increased for the remainder of that month of treatment.

### CLINICAL ASSESSMENT

Clinical features, including nude weight, were assessed daily during the control period, and then at one and four weeks of each treatment period. Exercise capacity was assessed on a treadmill, by means of a protocol in which low workloads were increased in six-minute stages.[10] Patients performed preliminary exercise tests during the control period until they achieved consistent maximal exercise. Maximal exercise time was measured at the end of the control period and at the end of each month of active treatment.

### HAEMODYNAMIC MEASUREMENTS

Patients were studied by means of standard right heart haemodynamic monitoring techniques.[11] Measurements were made of pulmonary artery end diastolic and right atrial pressures with the midchest as a zero reference point. Pulmonary artery end diastolic pressure was used as an indirect measure of left ventricular filling pressure. Blood pressure was measured by sphygmomanometer ($n=12$) or brachial artery catheter ($n=4$). Cardiac output was measured by thermodilution and the mean of at least three readings with less than 10% variation was used. Heart rate was measured from a simultaneous electrocardiogram. Mean blood pressure, cardiac index, and systemic vascular resistance were calculated by standard formulas.

In each study control measurements to assess haemodynamic stability were made over 30 minutes with the patient resting in bed. The patient then performed a symptom limited treadmill exercise test; haemodynamic measurements were made every six minutes at the end of each stage and during the minute of maximal exercise.

At the end of each month of treatment haemodynamic measurements were repeated, at rest and during treadmill exercise, two hours after medication.

### HORMONAL MEASUREMENTS

Plasma renin activity, aldosterone, noradrenaline, and vasopressin were measured during the control haemodynamic study and during the studies at the end of each month of treatment. Samples were taken at the same time as the last resting haemodynamic measurements and at maximal exercise. Samples were also taken at rest after one week on treatment, 2 hours after a maintenance dose of that month's drug. Venous blood was taken into cooled bottles, centrifuged immediately, and the plasma was stored at −70°C until assay.

Plasma renin activity and aldosterone were measured by radioimmunoassay[12 13] (normal ranges 0·5–2·5 ng/ml/h (0·39–1·9 nmol/l/h) and 100–600 pmol/l, respectively). We measured plasma noradrenaline by radioenzymatic assay using a modification (P Sever, personal communication) of Henry's method[14] (normal range 200–800 pg/ml (1·2–4·7 nmol/l)). Plasma vasopressin was measured by radioimmunoassay[15] (normal range: 0·4–1·6 μ units/ml (0·92–3·68 pmol/l)).

### PLASMA DRUG CONCENTRATIONS

Plasma captopril was not measured; increasing plasma renin activity was used as an indicator of effective converting enzyme inhibition. Plasma prazosin was measured by high pressure liquid chromatography.[16] Measurements were made before and two hours after a 4 mg maintenance dose in eight patients after one month's treatment.

### STATISTICAL ANALYSIS

The trial was designed to detect a change (p<0·05) in resting pulmonary artery end diastolic pressure of 5 mm Hg with a power of 0·80. The sample size required was calculated from data previously obtained in similar patients. Statistical analysis was by analysis of variance, Student's *t* tests for paired or unpaired data, as appropriate, and linear regression.[17 18] Preliminary analysis showed that order of treatment did not influence the changes in any variable[18]; results for the two treatment periods for each drug have therefore been combined to give a value of overall effect of that drug.

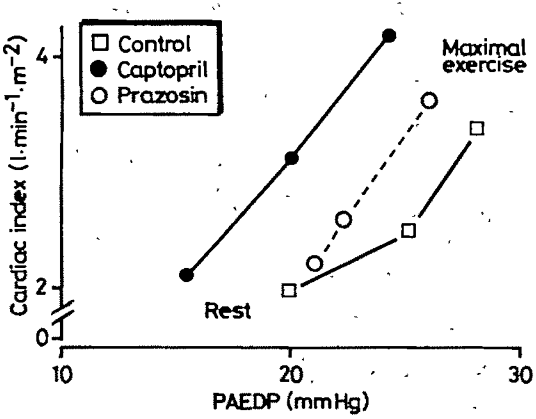

Fig 1 *Mean cardiac index and pulmonary artery end diastolic pressure (PAEDP) at rest, submaximal (6 min) and maximal exercise, in the control period, and after one month of captopril or prazosin in 16 patients. See text for statistical results, and Table 1 for variability.*

Results are given as the mean and 95% confidence limits. Hormonal values were only distributed normally after logarithmic transformation so geometric means are given for these results.

## Results

There were no significant changes in any variable during the placebo period or during the control periods before each haemodynamic study.

### CLINICAL EFFECTS

While on captopril 15 patients improved symptomatically, reporting a reduction in breathlessness and an increase in exercise capacity and general well-being; one patient did not improve. Mean weight fell by 1·6 kg (−3·2, −0·1 p=0·05) after one month, without any increase in diuretic dosage.

On prazosin five patients reported an initial improvement in symptoms, three were unchanged, and eight deteriorated. Peripheral oedema developed in six patients. During the month of treatment mean weight increased by 2·6 kg (+0·4, +4·9 p=0·03) despite an increase in the frusemide dosage in four patients who developed oedema after one week. Mean weight increased by 1·9 kg (+0·7, +3·1, p=0·04) even in the 10 patients who did not become oedematous.

Mean treadmill exercise time at the end of the placebo period was 17·5 min (12·0, 23·0); exercise was terminated by breathlessness in 11 patients, and by fatigue in five. Captopril increased exercise time by 6·2 min (+3·0, +9·5 p=0·001); four patients who had been limited by breathlessness were now limited by fatigue. Prazosin had no effect on exercise time (+0·7 min, −5·7, +7·0 p=0·81); eight patients were limited by breathlessness and eight by fatigue.

### HAEMODYNAMIC EFFECTS

The mean control pulmonary artery end diastolic pressure was 20 mm Hg at rest and increased to 28 mm Hg during exercise (p=0·0006) (Fig. 1, Table 1). After one month of prazosin this pressure was not significantly reduced either at rest or on exercise. After captopril, pulmonary artery end diastolic pres-

Table 1 *Haemodynamic results (mean (95% confidence limits)) at rest, submaximal and maximal exercise, in the control period, and after one month of captopril and prazosin in 16 patients. See text for statistical results*

| | *Rest* | *Submaximal exercise (6 min)* | *Maximal exercise* |
|---|---|---|---|
| | | *Pulmonary artery end diastolic pressure (mm Hg)* | |
| Control | 20 (17, 24) | 25 (20, 30) | 28 (23, 33) |
| Captopril | 16 (12, 20) | 19 (15, 24) | 24 (18, 28) |
| Prazosin | 22 (18, 25) | 22 (17, 26) | 26 (22, 30) |
| | | *Right atrial pressure (mm Hg)* | |
| Control | 5 (2, 8) | 7 (2, 12) | 9 (4, 14) |
| Captopril | 4 (2, 7) | 7 (3, 10) | 10 (5, 15) |
| Prazosin | 8 (4, 11) | 7 (3, 11) | 10 (6, 14) |
| | | *Cardiac index (l/min/m²)* | |
| Control | 2·0 (1·7, 2·3) | 2·6 (2·3, 2·9) | 3·5 (3·0, 4·0) |
| Captopril | 2·1 (1·9, 2·3) | 3·1 (2·8, 3·5) | 4·2 (3·7, 4·6) |
| Prazosin | 2·2 (1·9, 2·4) | 2·6 (2·4, 2·9) | 3·7 (3·2, 4·2) |
| | | *Heart rate (beats/min)* | |
| Control | 88 (81, 95) | 107 (98, 116) | 120 (110, 130) |
| Captopril | 80 (74, 87) | 100 (91, 109) | 122 (111, 132) |
| Prazosin | 84 (77, 91) | 98 (90, 107) | 116 (105, 127) |
| | | *Mean blood pressure (mm Hg)* | |
| Control | 84 (80, 89) | 89 (82, 96) | 89 (81, 96) |
| Captopril | 76 (69, 82) | 86 (81, 91) | 90 (83, 97) |
| Prazosin | 84 (79, 89) | 89 (81, 96) | 89 (82, 96) |
| | | *Systemic vascular resistance (dyn s cm⁻⁵)* | |
| Control | 1855 (1579, 2132) | 1519 (1274, 1765) | 1090 (882, 1299) |
| Captopril | 1549 (1337, 1762) | 1182 (1019, 1346) | 872 (724, 1014) |
| Prazosin | 1555 (1398, 1713) | 1360 (1172, 1549) | 940 (786, 1095) |

sure was reduced both at rest and during exercise ($p=0{\cdot}01$, $p=0{\cdot}05$), despite the greater exercise workload achieved. Right atrial pressure increased during the control exercise ($p=0{\cdot}009$); neither captopril nor prazosin altered right atrial pressure significantly.

The mean control cardiac index was 2·0 l/min/m$^2$ at rest, and this increased to only 3·5 l/min/m$^2$ with maximal exercise (Fig. 1). Prazosin caused no long term change in cardiac index, either at rest or on exercise. Captopril failed to increase resting cardiac index because, although it increased resting stroke volume index from a control value of 23 ml (20, 26) to 27 (23, 30 $p=0{\cdot}01$), it also reduced resting heart rate from 88 beats/min (81, 95) to 80 beats/min (74, 87 $p=0{\cdot}03$). During exercise on captopril, cardiac index was greater than the corresponding control values, both after six minutes (submaximal exercise, $p=0{\cdot}01$) and at maximal exercise ($p=0{\cdot}04$), because of a greater increase in stroke volume. Ventricular performance therefore improved at rest and on exercise with captopril but not with prazosin (Fig. 1).

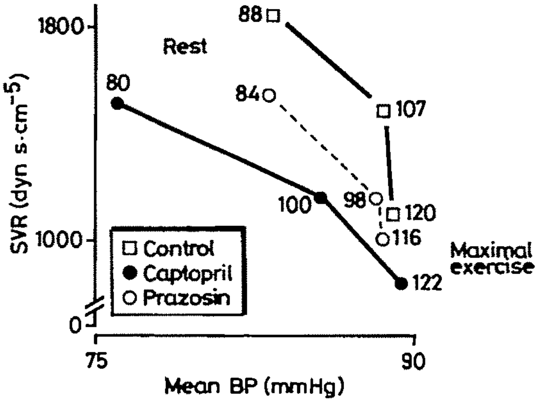

Fig 2 *Mean blood pressure (BP) and total systemic vascular resistance (SVR) at rest, submaximal (6 min) and maximal exercise, in the control period, and after one month of captopril and prazosin in 16 patients. Mean heart rate is shown alongside each point. See text for statistical results, and Table 1 for variability.*

The control mean blood pressure was normal at rest, and did not change significantly on exercise ($p=0{\cdot}13$) (Fig. 2). Prazosin caused no long term change in blood pressure, either at rest or on exercise. Captopril reduced mean blood pressure at rest ($p=0{\cdot}01$) but not during exercise.

The mean control systemic vascular resistance was raised at rest, and, although it fell during exercise ($p<0{\cdot}0001$), it remained abnormally raised at maximal exercise (Fig. 2), suggesting that vasodilatation during exercise was impaired. Arteriolar vasodilatation was maintained by both captopril and prazosin, with long term reduction in resting systemic vascular resistance ($p=0{\cdot}016$, $p=0{\cdot}04$). During submaximal and maximal exercise on prazosin, vascular resistance was not significantly different from control ($p=0{\cdot}24$, $p=0{\cdot}21$). During exercise on captopril, vascular resistance was lower than the corresponding control values, both at submaximal ($p<0{\cdot}0001$) and maximal exercise ($p=0{\cdot}04$).

Exercise time did not correlate with pulmonary artery end diastolic pressure at maximal exercise in

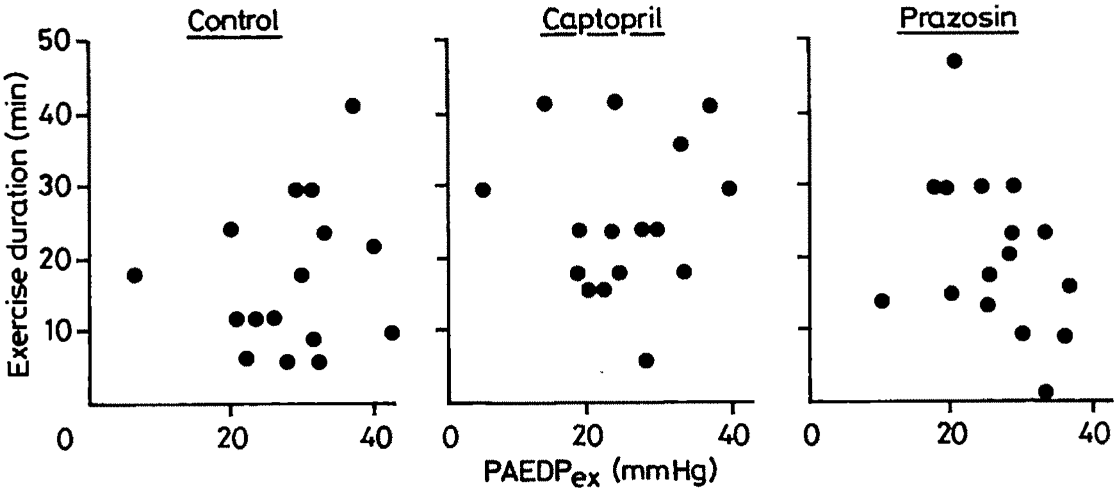

Fig. 3 *Lack of relation between mean pulmonary artery end diastolic pressure at maximal exercise (PAEDP$_{ex}$) and exercise time in the control, captopril, and prazosin periods.*

the control or treatment periods ($r < 0.37$) (Fig. 3), nor did changes in exercise time with treatment correlate with changes in pulmonary artery end diastolic pressure (Fig. 4). The change in systemic vascular resistance at maximal exercise from the control to the captopril period (representing improved vasodilatation), however, correlated inversely with the corresponding change in exercise time ($r = -0.61$, $p = 0.011$)—the greater the reduction in vascular resistance on exercise the greater the increase in exercise time. This relation was not seen during exercise in patients on prazosin ($p = 0.13$).

## HORMONAL EFFECTS

The mean control plasma sodium was 136 mmol/l (134, 138), and did not change during the study. The mean control urinary sodium excretion was 120 mmol/24 h (86, 154); repeat measurements after one

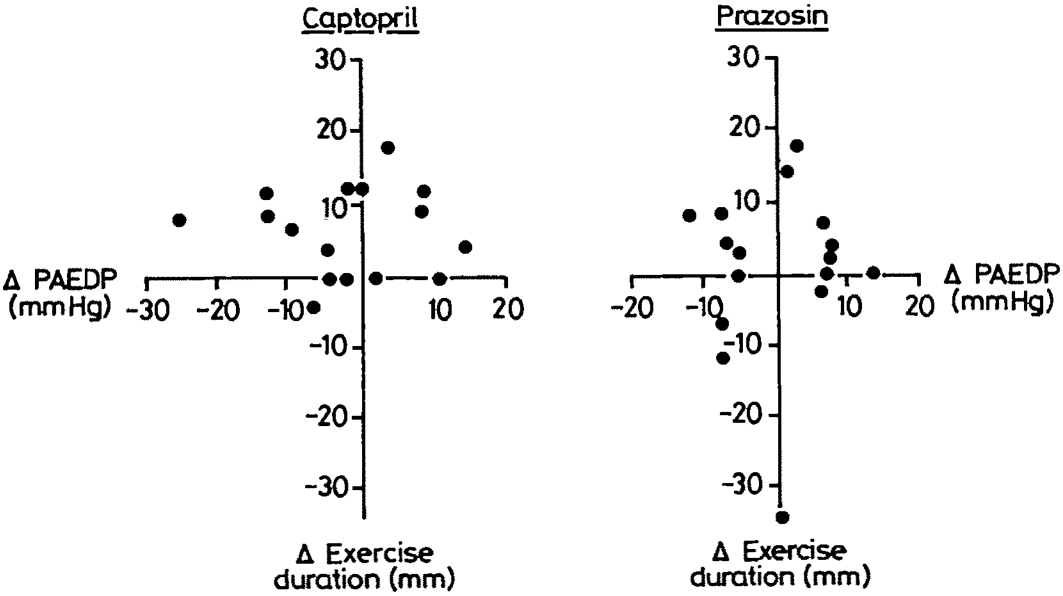

Fig. 4 *Lack of relation between the change of mean end diastolic pressure at maximal exercise (PAEDP) and the change of exercise time with either captopril or prazosin.*

month of each treatment were similar, indicating a stable sodium diet.

### RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

Control resting plasma renin activity and aldosterone were normal in four patients, but were raised in the remaining 12 (Table 2), correlating with resting pulmonary artery end diastolic pressure (r=0·58, p=0·02 and r=0·51, p=0·04 respectively) and with resting right atrial pressure (r=0·53, p=0·04 and r=0·77, p=0·001), but not with other resting variables (p>0·24).

During exercise, there were pronounced increases in plasma renin activity and aldosterone (p=0·0002, p<0·0001). Plasma renin activity at maximal exercise correlated with pulmonary artery end diastolic pressure and right atrial pressure at maximal exercise (r=0·61, p=0·01 and r=0·51, p=0·05).

Inhibition of angiotensin converting enzyme with captopril increased plasma renin activity at rest and on exercise (p=0·0006, p=0·02), and reduced plasma aldosterone both at rest and on exercise (p=0·02, p=0·04). During captopril treatment, ventricular filling pressures were unrelated to plasma renin activity or aldosterone.

Inhibition of the α adrenergic sympathetic system with prazosin increased resting plasma aldosterone after one week by 296 pmol/l (+150, +441 p=0·0009). After one month, however, when fluid retention and circulatory expansion had occurred, rest and exercise values of plasma renin activity and aldosterone were similar to control values, and correlated with ventricular filling pressures (r>0·5, p<0·04).

The changes in plasma aldosterone after one week's treatment with captopril and with prazosin correlated with the changes in body weight after one month on each drug (r=0·48, p=0·007).

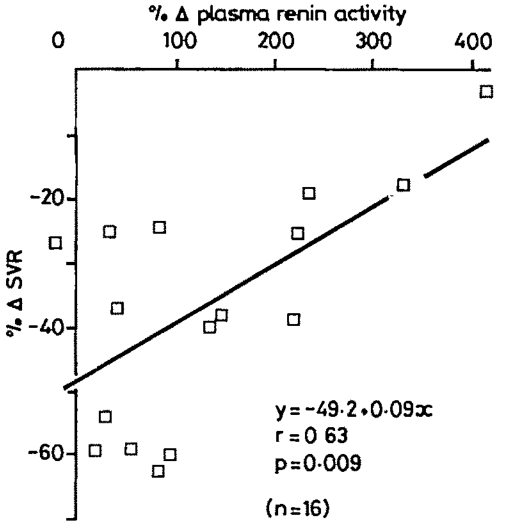

Fig. 5 *Relation between percentage changes from rest to maximal exercise in plasma renin activity and systemic vascular resistance in the control period*

In the control period, the exercise induced increase in plasma renin activity correlated inversely with the reduction in systemic vascular resistance on exercise (r=−0·63, p=0·0009) (Fig. 5); those patients with the greatest increase in plasma renin activity had the least vasodilatation on exercise, those with the least renin release achieved the greatest vasodilatation. This relation was no longer seen on captopril and systemic vascular resistance on exercise was lower than control values. On prazosin, the increase in plasma renin activity on exercise still

Table 2 *Hormonal values (geometric means (95% confidence limits)) at rest and maximal exercise, in the control period, and after one month of captopril and prazosin in 16 patients. See text for statistical results*

| | *Rest* | *Maximal exercise* |
|---|---|---|
| | *Plasma renin activity (ng/ml/h)* | |
| Control | 4·9 (3·0, 8·0) | 10·3 (6·7, 15·9) |
| Captopril | 15·2 (10·8, 21·3) | 22·3 (15·8, 31·7) |
| Prazosin | 5·3 (2·9, 9·6) | 11·1 (6·6, 18·5) |
| | *Plasma aldosterone (pmol/l)* | |
| Control | 689 (471, 1007) | 1189 (833, 1698) |
| Captopril | 454 (307, 673) | 901 (606, 1340) |
| Prazosin | 544 (352, 839) | 1236 (869, 1758) |
| | *Plasma noradrenaline (pg/ml)* | |
| Control | 1045 (781, 1398) | 2252 (1656, 3062) |
| Captopril | 859 (684, 1080) | 2215 (1584, 3097) |
| Prazosin | 1122 (888, 1418) | 2697 (2038, 3570) |
| | *Plasma vasopressin (μ units/ml)* | |
| Control | 0·81 (0·50, 1·29) | 1·61 (0·86, 3·0) |
| Captopril | 0·81 (0·46, 1·44) | 1·29 (0·74, 2·26) |
| Prazosin | 0·54 (0·33, 0·87) | 1·39 (0·79, 2·45) |

*Conversion: traditional units to SI*—renin: 1·0 ng/ml/h ≃ 0·77/mmol/l/h; noradrenaline 1 pg/ml = ≃ 0·0059 nmol/l; vasopressin: 1μ unit/ml = 2·3 pmol/l.

correlated inversely with the change in vascular resistance (r = −0·67, p = 0·002).

PLASMA NORADRENALINE

The control resting plasma noradrenaline was normal in five patients, but was raised in the remaining 11 (Table 2), and did not correlate with any single resting haemodynamic variable. Exercise caused a pronounced increase in plasma noradrenaline in all patients ($p<0\cdot0001$).

On captopril, resting plasma noradrenaline was reduced (p = 0·04). The pattern of increase of noradrenaline during exercise on captopril was similar to that during the control period (even though a greater workload was achieved) and correlated with the exercise induced increase in heart rate (r = 0·71, p = 0·002).

After one week of prazosin, resting plasma noradrenaline was increased by 371 pg/ml (+41, +702) (2·19 nmol/l: +0·24, +4 14) (p = 0·02), but after one month resting and exercise values were similar to control values.

During exercise in the control, captopril, and prazosin periods, the exercise induced increase in noradrenaline correlated inversely with the reduction in systemic vascular resistance on exercise (r = −0·62 p = 0 023; r = −0 67 p = 0·009; r = −0 72 p = 0·003 respectively). Those patients with the greatest increase in noradrenaline tended to have the least reduction in total systemic vascular resistance on exercise.

PLASMA VASOPRESSIN

The control resting plasma vasopressin was normal in all but three patients (Table 2), and did not correlate with plasma sodium or plasma osmolality or any haemodynamic variable. During upright exercise, plasma vasopressin increased in 12 patients (p = 0·03), but the peak value remained within the physiological range.

Prazosin caused no significant changes in vasopressin at rest or on exercise. During captopril treatment resting vasopressin was unchanged and there was no increase in vasopressin during exercise (p = 0·22) despite the greater workload achieved.

PLASMA PRAZOSIN CONCENTRATIONS

After one month's treatment, mean plasma prazosin concentration was 29·2 ng/ml (18, 41) (0·070 mmol/l: 0·043, 0·098) before a maintenance dose, increasing to 40·4 ng/ml (29, 52) (0·096 mmol/l: 0·069, 0·124) (t = 2·87 p = 0·02) two hours after a 4 mg dose. These drug concentrations are high, despite the relatively low dose of prazosin used, and could have resulted in prazosin inhibiting $\alpha_2$ as well as $\alpha_1$ adrenoceptors.

## Discussion

This is the first controlled study of interrelations between neuroendocrine systems, haemodynamic variables, and clinical characteristics both at rest and during upright exercise in the long term treatment of chronic heart failure.

The sympathetic and renin-angiotensin-aldosterone systems are usually activated in chronic heart failure,[19] to maintain blood pressure and perfusion of the cerebral and coronary circulations.[1 20] Renal, splanchnic, and cutaneous vasoconstriction occurs at rest and particularly during exercise, when the limited cardiac output must also supply an increased flow to working muscle. The vasodilatation that occurs in exercising muscle in healthy subjects is almost entirely due to local production of vasodilator metabolites, but in chronic heart failure this vasodilatation is impaired by mechanisms that are poorly understood.[20]

Homoeostatic neuroendocrine responses may have evolved to maintain the circulation during hypovolaemia and haemorrhage,[21] and to some extent they may support a failing circulation in heart failure. Maintained vasoconstriction and fluid retention, however, reduce ventricular performance.[22] Although directly acting vasodilating drugs can bring about short term haemodynamic improvement, long term clinical and haemodynamic benefit is often lacking,[23] possibly because of further neuroendocrine activation.[24]

To examine the roles of the renin-angiotensin-aldosterone and sympathetic systems in circulatory regulation in chronic heart failure, we performed a double blind, randomised cross over study to compare the effects of two neuroendocrine inhibitors, captopril and prazosin.[25 26] Captopril, an angiotensin converting enzyme inhibitor, causes vasodilatation by preventing the formation of angiotensin II, and it thus also reduces aldosterone secretion. Prazosin, an $\alpha_1$ adrenoceptor inhibitor, has acute vasodilator effects similar to those of captopril,[7] and causes venous and arteriolar dilatation by withdrawal of sympathetic activity. We studied only stable patients with mild to moderate heart failure (New York Heart Association class II–III), to permit measurements on exercise, and because in more severely ill patients hormonal abnormalities may be less important determinants of response to treatment than the natural progression of the disease itself.

Plasma renin activity, aldosterone, and noradrenaline were raised at rest in most patients, and increased further on exercise. It has been suggested that the renin system is activated in acute phases of heart failure but then returns to normal during stable chronic heart failure.[6] We found that the renin system was stimulated in chronic heart failure; it was not even suppressed in the patients who developed circulatory expansion on prazosin. Furthermore, patients who had near normal levels of plasma renin activity, aldosterone, or noradrenaline at rest developed greatly increased levels during exercise.

Several relations between hormonal, haemodynamic, and clinical variables were observed. Control ventricular filling pressures were raised and they correlated with plasma renin activity at rest and on exercise. Left ventricular filling pressures at maximal exercise did not correlate with exercise time, nor did any changes in filling pressures with treatment correlate with changes in exercise time. This lack of correlation between central haemodynamic variables and exercise capacity has been shown in other studies.[27 28]

Inhibition of the renin-angiotensin system by captopril reduced aldosterone and facilitated natriuresis, such that weight fell without an increase in diuretic dose. Left ventricular filling pressure fell both at rest and on exercise, and 15 patients reported a reduction in breathlessness. Plasma noradrenaline and heart rate were also reduced at rest on captopril, indicating some withdrawal of sympathetic activity.

Alpha adrenergic inhibition with prazosin caused vasodilatation which was associated with initial stimulation of the renin-angiotensin-aldosterone system and subsequent fluid retention, with oedema developing in six patients. Ventricular filling pressures were not reduced, and breathlessness improved in few patients.

The relation between vasopressin and ventricular filling pressures in heart failure is unclear. In the normal circulation, non-osmotic control reduces vasopressin release when atrial pressures increase, whereas in severe heart failure vasopressin release appears to occur independently of osmotic or non-osmotic control.[29] The patients in this study, with moderate heart failure, may illustrate an intermediate stage in the derangement of vasopressin control, since they had normal vasopressin concentrations at rest and on exercise, but these did not respond appropriately to changes in atrial pressures.

The total systemic vascular resistance in our patients was invariably raised, reflecting vasoconstriction in at least some vascular beds. Relations between vasoconstriction and neuroendocrine systems were studied by assessing the effects of exercise, before and in the presence of captopril and prazosin.

During the control period the reduction in systemic vascular resistance during exercise correlated inversely with increases in plasma renin activity and noradrenaline, suggesting that both angiotensin II and adrenergic mechanisms were limiting vasodilatation. Inhibition of $\alpha_1$ adrenoceptors with prazosin resulted in arteriolar vasodilatation at rest; during exercise it might have been expected that prazosin would facilitate vasodilatation by blocking $\alpha$ adrenoceptors and allowing unopposed stimulation of vasodilating $\beta_2$ receptors. The reduction in vascular resistance during exercise, however, was no greater than in the control period; it still correlated inversely with renin and noradrenaline release, and exercise capacity did not increase. Exercise capacity in chronic heart failure is related to nutritive muscle blood flow during exercise,[30] and is only poorly related to central haemodynamic variables.[27 28] Since prazosin caused vasodilatation at rest, but did not facilitate greater vasodilatation on exercise, or increase exercise capacity, our results can be interpreted as indirect evidence that prazosin did not increase muscle blood flow.

With inhibition of the renin-angiotensin system by captopril, systemic vascular resistance was reduced from control values both at rest and on exercise, even though plasma noradrenaline still increased. The change in systemic vascular resistance on exercise was no longer correlated with the change in plasma renin activity. The improved vasodilatation on exercise was associated with an increased exercise capacity, suggesting there had been an improvement in muscle blood flow.[30-32]

Although hormonal and haemodynamic changes occur immediately after administration of captopril, exercise capacity does not improve immediately, but increases progressively over a period of weeks.[33] Neither the acute changes in angiotensin II nor any acute haemodynamic changes can thus be directly responsible for the changes in exercise capacity. More long term changes in muscle blood flow on exercise are likely to be involved.

It has been suggested that the impairment of maximal vasodilatation in exercising muscle in heart failure is due to a "vascular stiffness factor", possibly related to the sodium content of the blood vessel wall.[19] Our study provides indirect evidence that angiotensin II may be such a factor, acting directly or indirectly through its effects on aldosterone and increasing the stiffness and sodium content of the vessel wall.

This study has established the important contribution of neuroendocrine systems in determining the haemodynamic and clinical features of chronic heart failure at rest and during exercise, and illustrates how inhibition of the renin-angiotensin-aldosterone system, in particular, can result in long term clinical improvement.

We thank Dr G A MacGregor (Charing Cross Hospital, London) for plasma renin activity and aldosterone assays, Prof P Sever (St Mary's Hospital Medical School, London) for noradrenaline assays, and Dr Mary Forsling (Middlesex Hospital Medical School, London) for vasopressin assays. Plasma prazosin was measured by D Stevenson (University of Surrey), courtesy of Pfizer Ltd. Prazosin and placebo were kindly supplied by Pfizer Ltd. Captopril and placebo were kindly supplied by Squibb UK Ltd.

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# Chronic anthracycline cardiotoxicity: haemodynamic and histopathological manifestations suggesting a restrictive endomyocardial disease

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SUMMARY Of 38 patients referred with suspected cardiotoxicity after administration of antineoplastic drugs, 11 patients with signs of manifest or latent anthracycline cardiotoxicity were selected for heart catheterisation with endomyocardial biopsy. Ultrastructural abnormalities of the myocytes with myofibrillar loss and cytoplasmic vacuolation were present in most patients and these findings were more pronounced in biopsy specimens from the left ventricle. Surprisingly, light microscopy showed considerable fibrous thickening of the endocardium in 10 of 11 patients, primarily in the left ventricle. These morphological findings together with the echocardiographic and the haemodynamic data suggest that chronic anthracycline cardiotoxicity is a restrictive endomyocardial disease. The biochemical mechanisms responsible for endocardial fibrosis are unknown, but drug induced damage to the endocardium, possibly mediated via hormonal or humoral agents, may feature in the initial phase of the toxic process. The present observations contribute toward the understanding of the pathophysiology of human anthracycline cardiotoxicity.

The clinical usefulness of daunorubicin and doxorubicin (Adriamycin) is limited by dose dependent cardiac damage (anthracycline cardiotoxicity).[1 2] Doxorubicin doses of up to 550 mg/m$^2$ body surface area (empirical cumulative dose) are usually not cardiotoxic. A subset of patients, however, shows signs of cardiac damage at lower doses, especially when there are contributory risk factors, for example, previous mediastinal irradiation.[3]

Limitation of the doxorubicin dose may deprive the patient of effective and extended cancer chemotherapy. Attempts to resolve this problem have included alterations of the dose schedule of doxorubicin and the development of analogues (class II anthracyclines) with reduced cardiotoxicity. Aclacinomycin (Aclarubicin)[4] and 4′-epidoxorubicin (Epirubicin)[5] are interesting new class II drugs. A safe maximum dose for both drugs has yet to be established; for Epirubicin it is probably about 1000 mg/m$^2$.

Various cardiological approaches have been used for the early detection of cardiac dysfunction during doxorubicin treatment. Apart from endomyocardial biopsy, they have proved to be of limited value.[6] In this context histological investigation of myocardial tissue is the most reliable method of monitoring heart function. It allows the total cumulative dose to be adjusted for the individual patient before obvious clinical signs of damage appear. The use of cardiac biopsy has, however, been restricted to centres with specialised histopathological facilities.[7 8] Fully developed anthracycline cardiotoxicity is usually described clinically as congestive cardiomyopathy.[1 2 9] In rare cases there is evidence of a restrictive pattern, but this has mainly been attributed to previous radiotherapy.[9 10] The present study was undertaken to describe severe human anthracycline cardiotoxicity. Our objectives were (*a*) to obtain a combined haemodynamic and histopathological classification of the condition, with both right and

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Accepted for publication 19 November 1985

left heart catheterisation data; (*b*) to confirm that myocardial inflammation is not a feature of severe human anthracycline cardiotoxicity,[3] despite this feature having been seen in animal experiments[11]; (*c*) to discover whether the morphological picture of cardiotoxicity seen during anthracycline chemotherapy[3] is different at the time of clinical heart failure, often when treatment has been discontinued (d) to determine, by examination of biopsy material, the ventricular wall in which morphological evidence of cardiotoxicity is most clearly expressed—that is, is the right ventricular septum a reliable sampling area?

## Patients and methods

Since 1980, 48 patients have been referred from various oncological/haematological departments in Copenhagen with suspected cardiotoxicity caused by antineoplastic drugs. The clinical manifestations of cardiotoxicity in the first 38 of these patients have been reported elsewhere.[12] The 11 selected patients described in the present report comprise all cases undergoing haemodynamic investigations with endomyocardial biopsy (during a two year period—from February 1982 to February 1984). There were eight women and three men, mean age 51 years (range 29–60). The indications for biopsy were overt congestive heart failure (manifest cardiotoxicity) (n=7); suspected anthracycline damage at less than the empirical dose (n=2); and to establish a means of cardiac monitoring during continued chemotherapy at doses in excess of the empirical dose (n=2).

Table 1 shows the initial patient characteristics with the following clinical data: the site of the primary neoplasm, risk factors, and cumulative anthracycline dose; and results from electrocardiographic and chest *x* ray examinations and the New York Heart Association functional class (when they were admitted for heart catheterisation). M mode and cross sectional echocardiograms were obtained with standard techniques.[13] We used gated blood pool scans (radionuclide angiocardiography) to measure left ventricular ejection fractions at rest and during supine submaximal exercise.[14]

Right and left heart catheterisation was performed and the cardiac index (Fick) was determined. Left ventricular angiocardiography and thoracic aortography were carried out. Transvascular endomyocardial biopsy specimens of the right ventricle or the left ventricle or both were obtained with King's bioptome[15] and a modified long sheath technique from the groin. A total of four to six biopsy specimens from each patient were fixed in formalin (10%) and processed for light microscopy (paraffin sections); in nine patients at least two samples were fixed in cacodylate buffered glutaraldehyde (3%) for later electron microscopy according to previously described techniques.[16] The histopathological evaluation and the electronmicroscopic grading, which corresponded to the Billingham scale[3] (that is 0, 1, 1·5, 2, 2·5, and 3) were performed without any knowledge of the clinical and haemodynamic data,

Table 1 *Clinical details of 11 patients with anthracycline cardiotoxicity*

| *Patient No* | *Age* | *Sex* | *Diagnosis* | *Risk factors* | *Total dose of anthracycline* | *NYHA class* | *ECG* | *Chest x ray* | *Outcome* |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 33 | F | Pancreatic carcinoma | — | Doxorubicin 550 mg/m² | I | ST | No cardiomegaly | Died of cancer |
| 2 | 49 | M | Lung carcinoma | — | 4'-epidoxorubicin 360 mg/m² | II | Negative T waves | No cardiomegaly | Died of cancer |
| 3 | 55 | F | Breast carcinoma | Irradiation, cyclophosphamide | Doxorubicin 575 mg/m² | IV | ST and low R waves | Cardiomegaly | Sudden death |
| 4 | 59 | F | Parotid carcinoma | — | Doxorubicin 550 mg/m² | I | ST and low R waves | No cardiomegaly | Died of cancer/ CHF |
| 5 | 29 | F | Soft tissue sarcoma | Cyclophosphamide | Doxorubicin 550 mg/m² | IV | ST and low R waves | Cardiomegaly | Alive NYHA I |
| 6 | 58 | F | Ovarian carcinoma | Cyclophosphamide | Doxorubicin 530 mg/m² | IV | ST and low R waves | (Cardiomegaly) | Alive NYHA II |
| 7 | 55 | M | Lung carcinoma | — | 4'-epidoxorubicin 1533 mg/m² | III | ST and low R waves | No cardiomegaly | Died of cancer/ CHF |
| 8 | 57 | F | Ovarian carcinoma | Cyclophosphamide | Doxorubicin 564 mg/m² | II | SR and low R waves | No cardiomegaly | Alive NYHA I |
| 9 | 53 | F | Ovarian carcinoma | Cyclophosphamide | Doxorubicin 550 mg/m² | II | ST and negative T waves | (Cardiomegaly) | Sudden death |
| 10 | 60 | M | Lung mesothelioma | Arterial hypertension | Doxorubicin 550 mg/m² | II | ST and low R waves | (Cardiomegaly) | Alive NYHA I |
| 11 | 53 | F | Lung carcinoma | — | 4'-epidoxorubicin 645 mg/m² | II | SR and negative T waves | (Cardiomegaly) | Died of cancer? |

ST, sinus tachycardia; SR, sinus rhythm, CHF, congestive heart failure; NYHA, New York Heart Association. Parentheses indicate presence of slight cardiomegaly.

Table 2 *Echocardiographic, scintigraphic, and haemodynamic data in 11 patients with anthracycline cardiotoxicity*

| Patient No | EDD (cm) | ESD (cm) | MSS (cm) | RV (cm) | LA (cm) | Gated scan | | RA (mm Hg) mean | Systolic/diastolic pressure | | | Angiography LVEF (%) | Cardiac index (l/min/m²) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | LVEF (%) (rest) | LVEF (%) (exercise) | | RV (mm Hg) | PA (mm Hg) | LV (mm Hg) | | |
| 1 | 4·2 | 3·0 | 0·4 | 2·0 | 2·5 | — | — | 2 | 28/3 | 26/8 | 105/3 | — | (5·2) |
| 2 | 5·3 | 3·5 | 0·5 | 2·3 | 3·3 | — | — | 5 | 34/7 | 34/15 | 115/7 | 59 | 3·8 |
| 3 | 5·5 | 4·6 | 2·0 | 2·7 | 4·0 | 19 | 23 | 2 | 35/2 | 30/13 | 90/11 | — | 1·4 |
| 4 | Impossible: lung metastases | | | | | 47 | 47 | 0 | 24/0 | 19/8 | 118/2 | 35 | 3·3 |
| 5 | 5·3 | 4·5 | 1·2 | 3·0 | 3·5 | 17 | 21 | 12 | 37/12 | 38/21 | 85/22 | 23 | 1·6 |
| 6 | 5·8 | 5·1 | 2·2 | 1·8 | 4·6 | 18 | 18 | 0 | 23/3 | 24/10 | 85/19 | 18 | 2·4 |
| 7 | 5·0 | 4·2 | 1·0 | 2·2 | 2·8 | 40 | 40 | 0 | 21/1 | 19/6 | 85/4 | 33 | 2·9 |
| 8 | 5·1 | 4·1 | 1·3 | 1·8 | 2·3 | 33 | 38 | 1 | 17/1 | 28/10 | 100/4 | 41 | 2·1 |
| 9 | 5·1 | 4·3 | 1·5 | 1·5 | 2·6 | 41 | 45 | 0 | 27/3 | 27/10 | 115/15 | 51 | 3·6 |
| 10 | 5·5 | 5·0 | 1·5 | 1·3 | 3·8 | — | — | 0 | 22/1 | 22/8 | 115/11 | 44 | 1·6 |
| 11 | Impossible: lung metastases | | | | | 38 | 43 | 9 | 30/10 | 28/12 | 80/13 | — | 2·5 |

EDD, left ventricular end diastolic diameter; ESD, left ventricular end systolic diameter; MSS, mitral septal separation; RV, right ventricle; LA, left atrium; RA, right atrium; PA, pulmonary artery; LVEF%, left ventricular ejection fraction.

apart from the information that the patient had been treated with an antineoplastic drug. These grades are essentially: (1) occasional isolated myocytes showing myofibrillar loss or sarcoplasmic swelling; (2) more widespread changes with clusters of affected myocytes; (3) necrotic cells with nuclear and mitochondrial degeneration. Although fibrosis is a myocardial sequela of doxorubicin treatment, it is not used in the scoring because it is a non-specific reaction that can also be a side effect of radiation treatment.

Informed consent was obtained from all patients before the invasive diagnostic procedures.

## Results

Eight patients had been treated with doxorubicin and three with a derivative (4′-epidoxorubicin) for three weeks. Seven patients received combination chemotherapy with cyclophosphamide and/or 5-fluorouracil or vincristine. The mean cumulative doxorubicin dose was 552 mg/m² body surface area (range 530-575 mg). The 4′-epidoxorubicin dose in patients 2, 7, and 11 was 360, 1533, and 645 mg/m² respectively. Table 2 shows the echocardiographic, scintigraphic, and catheterisation data.

### ECHOCARDIOGRAPHIC DATA

Echocardiograms in nine patients generally showed modest dilatation of the left ventricle especially at end systole (mean 4·3 cm), whereas the diameter at end diastole was generally normal (mean 5·2 cm). There was also considerable reduction in contractility and asynchronous or paradoxical septal movement (Fig. 1). Small pericardial (two patients) or pleural effusions (two patients) were also seen. In two patients the echocardiograms were poor because of lung metastases, and further calculations were impossible.

### SCINTIGRAPHIC AND ANGIOGRAPHIC DATA

Left ventricular ejection fractions calculated from the gated blood pool scans ranged from 18% to 47% (mean 32%); these values were unchanged during subsequent supine exercise (at a maximum workload of 50 W). Left ventricular cineangiograms in

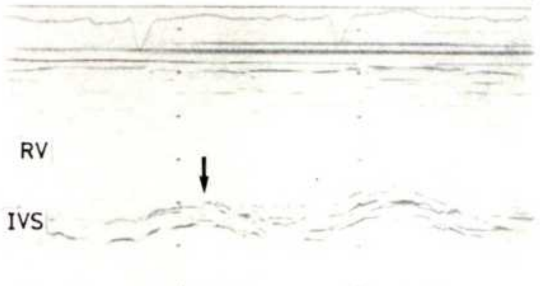

Fig. 1 *M mode echocardiogram from case 5. The left ventricle (LV) is moderately enlarged at end systole with increased mitral-septal separation and reduced contractility. The numerical result for fractional shortening (probably about 15%) is unreliable because of paradoxical septal movement (arrow). RV, right ventricle; IVS, intraventricular septum; PW, posterior wall of left ventricle.*

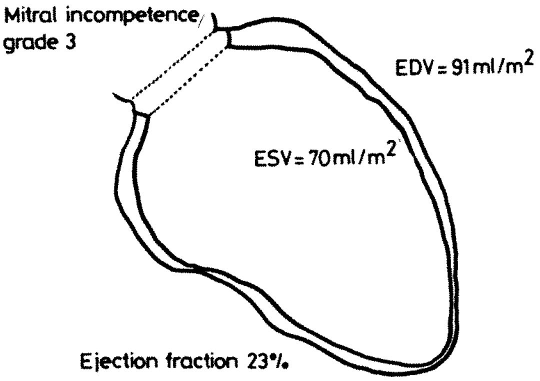

Fig. 2 *End systolic and end diastolic frames from the left ventricular angiograms of case 5 showing a poorly contracting ventricle with an ejection fraction of 23%. Severe mitral regurgitation (grade 3/4) was present despite the ventricle being only moderately dilated. EDV, end diastolic volume; ESV, end systolic volume.*

eight patients showed a rigid contraction pattern in two and severe mitral incompetence in one (case 5) (Fig. 2). None of the patients showed clinical evidence of concomitant ischaemic heart disease—that is they did not have angina pectoris or myocardial infarction. Non-selective coronary arteriography obtained during contrast injection of the aortic root did not show any evidence of important lesions of the major epicardial coronary arteries.

### PRESSURE MEASUREMENTS

In nine of the 11 patients pressure tracings obtained during catheterisation showed a pseudo-dip and plateau configuration in diastole[17 18] in the left or the right ventricle or both (Fig. 3). Right ventricular early diastolic dip was seen in five patients, and a diastolic plateau was indicated in two. Seven patients showed diastolic dip in the left ventricle and one patient showed a tendency to a plateau. There was a diastolic dip in three patients and a suggestion of a plateau in one, in the pressure curve from both ventricles. Prominent a waves,[17] (that is "atrial kick", an indirect indication of reduced ventricular compliance) were seen in nine of 11 patients; in the right ventricle in four, in the left ventricle in two, and in both ventricles in three.

### ENDOMYOCARDIAL BIOPSY DATA

*Light microscopy* of cardiac biopsy specimens showed considerable fibrous thickening of the endocardium in 10 of the 11 patients, particularly in samples from the left ventricle (Table 3). Only four of eight patients had some degree of endocardial fibrosis in samples of the right ventricular septum. The endocardial thickening was due to collagenous tissue, possible with some smooth muscle cell deposition (Fig. 4). No inflammatory cells were seen in the endocardial zone, and organised mural thrombi were only seen in the left ventricle of one patient (case 4). The myocardium was generally characterised by cellular hypertrophy (both fibres and nuclei) and concomitant attenuation. The myocytes were regularly arranged without signs of disarray. Degenerative changes (with loss of myofibrils and vacuolation of the cytoplasm) were seen in the most severe cases, such as case 3. The amount of interstitium was generally increased; in case 3 replacement fibrosis was also seen. The vessels appeared to be normal, and there were no signs of inflammation.

*Electron microscopic* studies of biopsy material from nine patients generally showed swelling and increased numbers of mitochondria (Fig. 5). Nuclear crenation, intracellular oedema, and mitochondriosis were non-specific, since similar changes were seen in biopsy specimens in two male controls (aged 50 and 47 years) before start of chemotherapy.

Table 3 *Endomyocardial biopsy data in 11 patients with anthracycline cardiotoxicity*

| *Patient No* | *Sampling sites* | | *Morphological grade* | *Endocardial thickening* | | *Mitochondriosis* | *Myofibrillar drop out* | *Sarcotubular swelling* | *Deformation of nuclei* |
|---|---|---|---|---|---|---|---|---|---|
| | *RV* | *LV* | | *RV (μm)* | *LV (μm)* | | | | |
| 1 | + | + | 1 (focal LV) | — | — | Slight | Slight | — | Moderate |
| 2 | + | + | 1 (focal LV) | — | 60–100 | Slight | Slight | — | Slight |
| 3 | + | + | 3 (widespread LV) | 60–100 | >100 | Moderate | Slight | Slight | Severe |
| 4 | + | + | 1 (focal LV) | 20–60 | 60–100 | Severe | Moderate | Slight | Moderate |
| 5 | + | + | 1·5 (focal RV and LV) | — | 60–100 | Moderate | Moderate | — | Slight |
| 6 | – | + | 2·5 | | 60–100 | Severe | Moderate | Slight | Moderate |
| 7 | + | + | 2·5 (widespread LV) | 20–60 | >100 | Moderate | Severe | Moderate | Moderate |
| 8 | + | + | 3 (focal LV) | — | 60–100 | Moderate | Moderate | — | Moderate |
| 9 | + | + | 1* (focal LV) | 20–60 | 60–100 | | | | |
| 10 | – | + | 2·5* | | >100 | | | | |
| 11 | – | + | 1 | | 20–60 | Moderate | Slight | — | Slight |

*Light microscopy.
RV, right ventricle; LV, left ventricle.

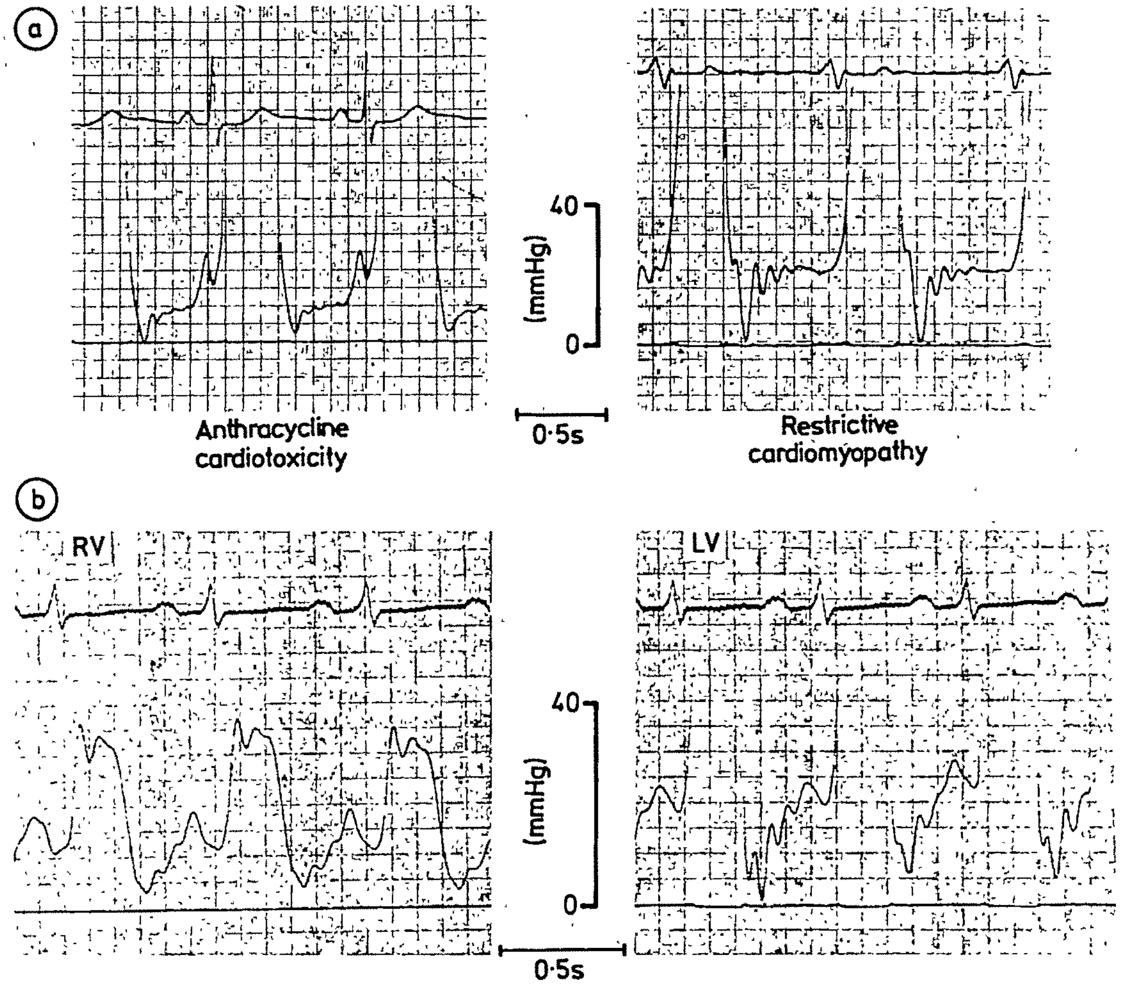

Fig. 3 *(a) Left ventricular pressure tracings from case 8 with doxorubicin cardiotoxicity (left) and a 36 year old woman with restrictive cardiomyopathy (right). There is a tendency to a diastolic dip and plateau configuration in case 8. The a wave is not present in the curve from the idiopathic case (right) with atrial fibrillation. (b) Pressure tracings from case 5 showing a waves and protodiastolic dip in the left ventricle. RV, right ventricle; LV, left ventricle.*

Such changes have been shown to be non-specific markers of cardiac hypertrophy.[19] Disruption of the myofibrils and myofibrillar "drop out" were seen in eight patients (Fig. 6) and four patients showed focal sarcotubular swelling (Fig. 7)—all characteristic signs of chronic anthracycline cardiotoxicity.[3]

## HISTOLOGICAL FINDINGS IN THE LEFT AND RIGHT VENTRICLES

In eight patients in whom bilateral biopsy specimens were obtained, morphological damage was more pronounced in the left ventricle; this was especially true of endocardial thickening (in seven of eight cases) and also myocardial changes (in four of eight cases). Four patients had a normal right ventricular endocardium, and in one (case 8) the right ventricular biopsy specimens were completely normal, whereas the left ventricular biopsy specimens showed moderate damage. The most severe endocardial fibrosis of the left ventricle (408 $\mu$m; normal thickness $<20\,\mu$m[16]) was seen in a patient (case 3) who had had radiation to the mediastinum.

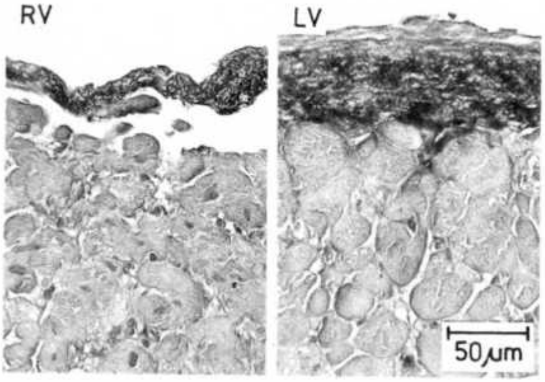

Fig. 4 *Photomicrograph of endomyocardial biopsy specimens from case 5 showing normal endocardium in the right ventricle (RV) and fibrous thickening of the endocardium in the left ventricle (LV). (elastic van Gieson stain.)*

NECROPSY MATERIAL

Tissue was obtained from a patient (case 1) who died of pancreatic carcinoma in hospital one week after catheterisation. The histological appearance of the endomyocardial biopsy specimens from this patient correlated well with the degree of damage observed in multiple sections from the myocardium (Billingham grade 1).

## Discussion

In this study we have attempted to define the haemodynamic and histological features that are typical

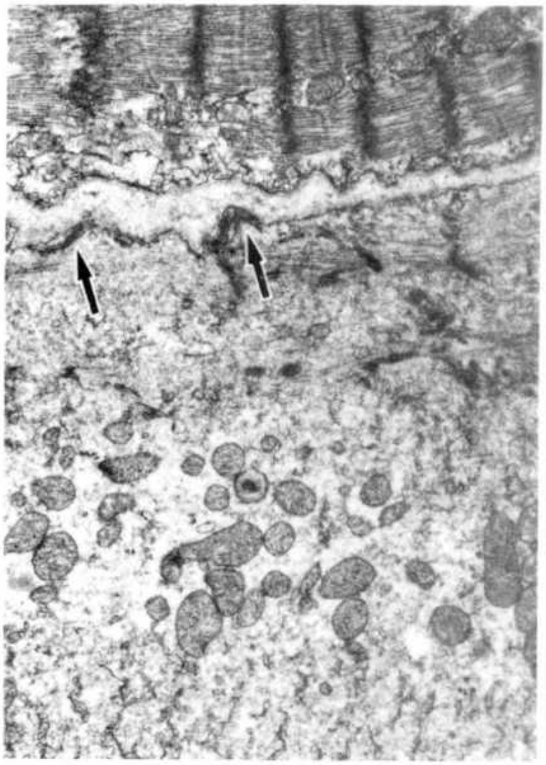

Fig. 6 *Electron micrograph (case 6) showing a myocyte with preserved myofibrils at the top, and at the bottom myocytic degeneration with myofibrillar loss and small z band fragments (arrows) along the inner cell membrane (z band lateralisation) (× 4800).*

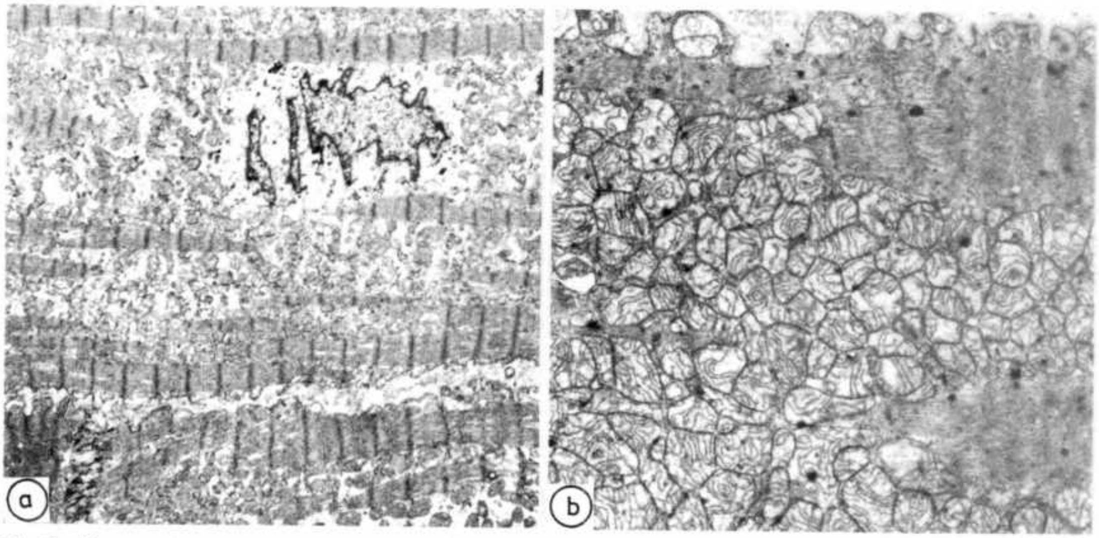

Fig. 5 *Electron micrographs of an endomyocardial biopsy specimen from case 6 showing: (a) nuclear crenation, increased number of mitochondria (mitochondriosis), and some intracellular oedema (× 1500); (b) mitochondriosis at a higher magnification (× 4800) in another area.*

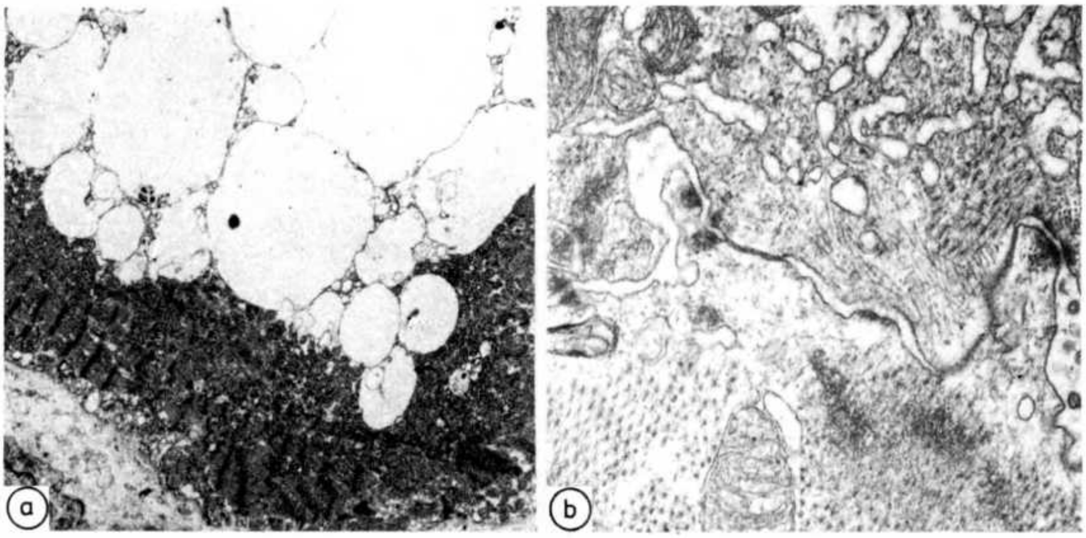

Fig. 7 *Electronmicrographs of endomyocardial biopsy specimens from case 7 showing: (a) a single myocyte with extreme dilatation of the sarcotubular system (toluidine blue × 1000); and (b) the presence of the same feature, but to a lesser degree, at the level of an intercalated disc (× 20 000).*

of clinically overt anthracycline cardiotoxicity. The prognosis of patients with this iatrogenic disorder is poor[2] and many are almost untreatable.

As in a previous study,[3] we found no evidence of acute or chronic inflammation in the endomyocardial biopsy specimens and we therefore did not use immunosuppressants.[20] Morphological investigations of endomyocardial biopsy material from the right ventricular septum are a reliable means of monitoring cardiac damage during anthracycline treatment. Such monitoring has meant that some patients have been able to receive over 1000 mg/m$^2$ of doxorubicin.[21]

Myocytic changes, which are most clearly seen by electron microscopy, are the characteristic histopathological features of doxorubicin damage. The density of these lesions correlates linearly with cumulative dose. Their severity has been graded on the Billingham score[3] on a scale from 0 (no cells affected) to 3 (severe morphological damage).

Data obtained during right heart catheterisation (at rest and during exercise) suggest a non-linear (parabolic) relation between electronmicroscopic changes and the degree of haemodynamic impairment. Some degree of tissue damage may be present without equivalent haemodynamic signs of impairment, and heart failure occurs only at a certain critical morphological threshold.[22] These myocardial doxorubicin lesions, which have been useful for adjusting the dosage of doxorubicin in individual patients, were present in most of our patients. Thus, the electronmicroscopic picture usually found during the period of doxorubicin treatment[3 7] had not disappeared when our patients were investigated mean 2·7 months (range 0–5·5) after discontinuation of chemotherapy. Apparently, biopsy grading of cardiac damage based on material from the right ventricle[21-23] is the most sensitive and specific method for assessing doxorubicin cardiotoxicity. Eight of our patients had biopsy examination of both ventricles, and the degree of myocardial damage was most pronounced in samples from the left ventricle. This suggests that a false negative assessment may be obtained if biopsy specimens are taken only from the right ventricular septum.

Surprisingly, results from all but one patient showed pronounced fibrous thickening of the endocardium, a disorder which was most pronounced in the left ventricle (means 48 $\mu$m and 138 $\mu$m in the right and left ventricles, respectively). This observation had already been made indirectly in the catheterisation laboratory at biopsy when it was rather difficult to excise tissue specimens with the bioptome. The mechanisms by which anthracycline cardiotoxicity leads to endocardial fibrosis are obscure. Until now endocardial fibrosis has been described in only a few case reports,[9 10] and such damage may have been attributed to radiation damage. Only one of our patients (case 3) had received radiation therapy, however; this patient had the most pronounced endocardial fibrosis. Methysergide has been reported to cause endomyocardial fibrosis,[24] as has long term treatment with certain antineoplastic drugs such as busulfan[25] in rare cases.

The explanation that endocardial thickening is secondary to dilatation of the ventricles, which is a common finding in dilated cardiomyopathy,[16] is certainly inadequate in our patients who had only modest cavity enlargement. Endocardial lesions with a patchy distribution may resemble the changes seen in carcinoid heart disease that seem to be related to an excess of circulating serotonin.[26] Hormonal mechanisms, such as histamine mediated damage,[27] may have been involved in anthracycline related endocardial fibrosis in our study, in which left ventricular involvement predominated (unlike the predominantly right ventricular involvement found in carcinoid heart disease).

Eosinophilic cells, which are found in endocardial fibrosis caused by Loeffler's endomyocardial disease,[28] were not detected in our biopsy specimens. In Loeffler's endomyocardial disease damage is apparently caused by eosinophilic cationic proteins. Cardiotoxic factors produced by certain tumours, such as circulating humoral substances, may be one of the factors giving rise to both myocardial and endocardial lesions.[29]

To our knowledge this is the first published report of endocardial fibrosis in a series of patients who have had anthracycline treatment. The value of a diagnosis of endocardial thickening in monitoring cancer patients during treatment with anthracyclines remains to be established. Endocardial thickening may, however, be the first morphological sign of cardiotoxicity. This accords with reports that myocardial changes first appear in the subendocardium (Billingham ME, personal communication). Our data and the outcome of treatment of heart failure in cases of overt cardiotoxicity, do not suggest that endomyocardial biopsy has any recognisable consequences. The procedure seems justified only in cases of latent cardiotoxicity[12] when the possible development of chronic cardiotoxicity is being considered. We found that initial clinical status (New York Heart Association functional class) correlated with morphological grading (Billingham score)—that is the higher the pathological score the worse the clinical status (Tables 1 and 3).

The endomyocardial data and echocardiographic findings (that is a modest dilatation of the left ventricle) and the pressure curves seem to indicate that overt anthracycline cardiotoxicity is to some extent a restrictive endomyocardial disease. This may have therapeutic implications. For example vasodilator agents should be given with caution. Conversely, coenzyme Q-10 may be used without additional risk to improve cardiac function.[30]

## CONCLUSION

Chronic anthracycline cardiotoxicity, which has been classified as a dilated heart disease (mimicking congestive cardiomyopathy), seems to be characterised by pronounced endocardial fibrosis. Morphological observations, mainly from the left ventricle of patients who had not received radiotherapy, together with echocardiographic and haemodynamic data, suggest that anthracyclines can mediate a toxic endocardial disorder. When this heals restrictive endomyocardial disease develops in parallel with certain characteristic myocardial effects. Pronounced endocardial fibrosis, however, has been seen in patients with low grade myocardial damage; and the changes may not be detected when investigations are made of the right ventricle only. The present observations may contribute to the understanding of the obscure pathogenesis of anthracycline cardiotoxicity, and may be useful in modifying the treatment of patients with anthracycline induced heart failure.

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*Br Heart J* 1986; 55: 283–5

# Non-invasive grading of aortic regurgitation by Doppler ultrasonography

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SUMMARY Doppler ultrasound without concomitant echocardiographic imaging was used to grade isolated aortic regurgitation in 21 patients. The severity of aortic regurgitation was subsequently graded (from 0 to IV) angiographically.

A 2 MHz continuous wave Doppler transducer was placed over the apex of the heart and the beam was aimed parallel to the mitral flow by means of acoustic guidance. Mitral pressure half time was calculated from the analogue maximum velocity tracing and it was $\leqslant 60$ ms in 10 controls; 50–120 ms in five patients with grade II, 120–160 ms in nine patients with grade III, and $\geqslant 160$ ms in seven patients with grade IV aortic regurgitation.

These results indicate that a semi-quantitative grading of aortic regurgitation may be obtained non-invasively with non-imaging Doppler ultrasonography in patients without concomitant mitral valve disease.

In patients with severe aortic regurgitation the presystolic murmur described by Austin Flint in 1862 presumably results from impairment of mitral flow by the aortic regurgitant jet impinging on the mitral valve.[1] Because intracardiac blood flow can be measured non-invasively by Doppler ultrasonography,[2] we investigated the possibility of predicting the severity of aortic regurgitation on the basis of mitral flow measured by the Doppler method.

## Patients and methods

### PATIENTS

We studied 21 patients with aortic regurgitation (15 men, 6 women, aged 27–74 years). Patients with rheumatic mitral valve disease were excluded by echocardiography. All patients underwent subsequent left heart catheterisation and biplane aortography for visual grading of aortic regurgitation by an independent observer (grade 0, no regurgitation; grade I, faint regurgitation; grade II, frank regurgitation without accumulation of contrast material within the left ventricle; grade III, regurgitation and accumulation of contrast; grade IV, free regurgitation with immediate opacification of the entire left ventricle). We also studied 10 controls without valvar heart disease.

### DOPPLER TECHNIQUE

A 2 MHz continuous wave ultrasound transducer without imaging capability was placed over the apex of the heart, with the ultrasonic beam aimed towards the mitral orifice and kept parallel with the mitral blood flow by means of acoustic guidance. The Doppler instrument (Pedof, Vingmed, Oslo) is equipped with frequency estimators, providing analogue outputs of non-directional maximum flow velocity ($V_{max}$) and directional mean velocity ($V_{mean}$). When the typical diastolic audiosignal of mitral flow was heard, simultaneous recordings of electrocardiogram, $V_{mean}$, and $V_{max}$ were made at 50 mm/s paper speed. The mitral pressure half time (t/2) was determined from the $V_{max}$ recordings—that is the time required for $V_{max}$ at its peak diastolic value (A) to reach the point $B = A/\sqrt{2}$ (Fig. 1). t/2 has been shown to correlate inversely with the area of the mitral valve orifice in patients in whom mitral flow is impaired by mitral stenosis.[2 3]

### STATISTICAL ANALYSIS

Doppler and angiographic data were compared by the non-parametric rank correlation method of Kendall.[4]

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Accepted for publication 22 October 1985

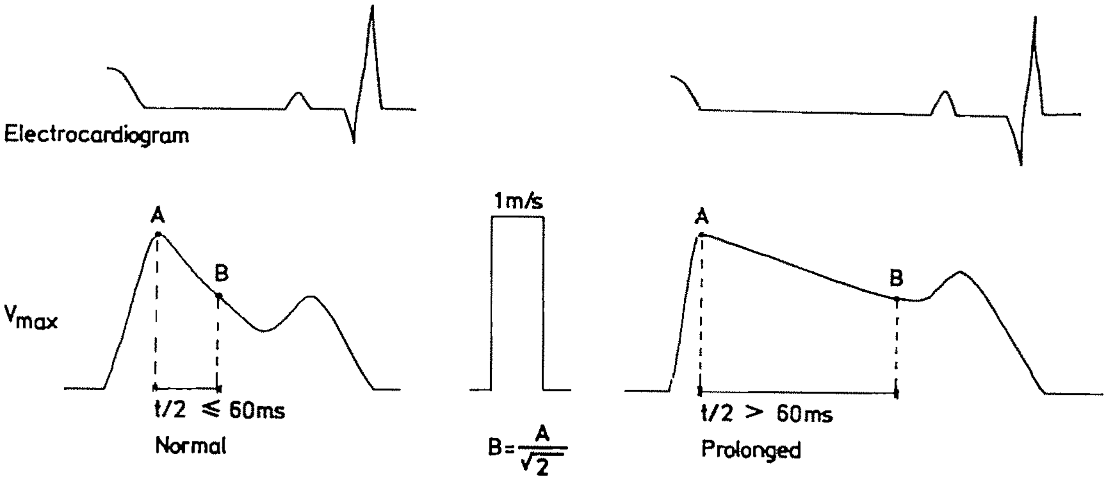

Fig. 1 *Schematic representation of normal mitral flow (left) and prolongation of mitral pressure half time (t/2) (right). $V_{max}$, maximum flow velocity.*

## Results

Mitral pressure half time was ≤60 ms in all controls, whereas it was 50–120 ms in the five patients with grade II aortic regurgitation; 120–160 ms in the nine patients with grade III aortic regurgitation; and ≥160 ms in the seven patients with grade IV aortic regurgitation (Figs. 2 and 3). There was a highly significant correlation between the angiographic and Doppler grading (Kendall's rank correlation test, $p<0{\cdot}001$). Left ventricular end diastolic pressures ranged from 8 mm Hg to 44 mm Hg. There was no correlation between t/2 and left ventricular end diastolic pressure. An Austin Flint murmur was detected clinically in eight of 16 patients with grade III or IV aortic regurgitation.

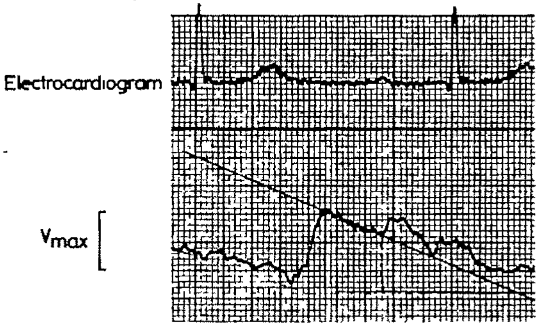

Fig. 2 *Prolonged mitral pressure half time (200 ms) as measured on the mitral maximum flow velocity curve in a patient with severe aortic regurgitation (angiographic grade IV) (calibration = 1 m/s; paper speed = 50 mm/s).*

## Discussion

Non-invasive grading of aortic regurgitation has been unrewarding in the past. Because the aortic regurgitant jet can be detected directly by Doppler

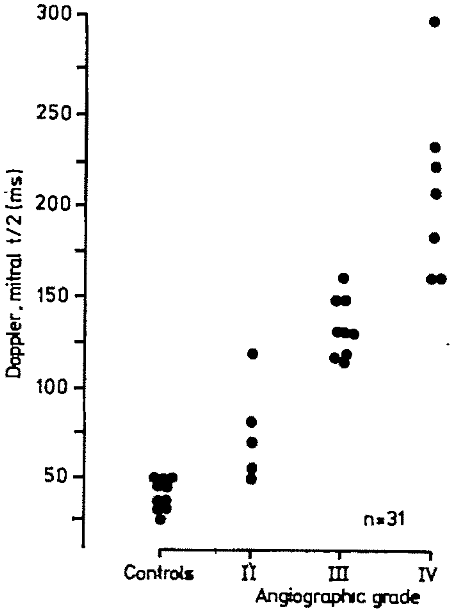

Fig. 3 *Comparison of mitral pressure half time (t/2) as measured by the non-invasive Doppler method and angiographic grade of aortic regurgitation in 21 patients with aortic regurgitation and in 10 controls ($p<0{\cdot}001$ by Kendall's rank correlation test).*

ultrasound techniques there have been several attempts at quantitation. Boughner calculated a regurgitant fraction from planimetric comparison of forward-to-reverse flow curves.[5] A similar approach was used by Sequeira and Watt[6] and by Quinones *et al*,[7] whereas Diebold *et al* reported the use of a forward-to-reverse velocity index.[8] The usefulness of these methods is limited primarily by the considerable overlap of data and by the difficulty of obtaining adequate simultaneous tracings of systolic and diastolic flow curves. Jenni *et al* showed that the use of multiple gates (pulsed wave mode) provides a better basis for measurement of flow.[9] This technique, however, is experimental. Ciobanu *et al* reported a different technique with mapping of the left ventricular outflow tract to detect the presence of aortic regurgitant flow, and the results of this method accorded well with angiographic grading.[10] Their method needs to be confirmed.

We used the simple and inexpensive technique of continuous wave Doppler without concomitant echocardiographic imaging. The impairment of diastolic flow through the mitral orifice was used as a measure of aortic regurgitation. Prediction of the angiographic severity of aortic regurgitation by this method was good (Fig. 3). Most authorities agree that though there may be early closure of the mitral valve in cases of acute aortic regurgitation, this is not likely to be responsible for the Flint murmur in all cases. The Flint murmur seems to arise rather as a result of turbulence generated between mitral and aortic flows in diastole.[11]

Alteration of mitral flow can only be used as a measure of aortic regurgitation in patients without mitral valve disease because in mitral stenosis the duration of t/2 is inversely related to the mitral valve area.[3] Also in patients with severe aortic regurgitation clear recordings of mitral flow are sometimes difficult to obtain because of excessive turbulence. Indeed, mitral $V_{max}$ tracings were difficult to record in some of our patients. Normal mitral flow does not entirely rule out important aortic regurgitation because the regurgitant jet may be diverted more towards the left ventricular posterior wall and thus avoid the mitral inflow. Care must also be taken to avoid the aortic regurgitant jet. This is accomplished by searching for the typical biphasic pattern of mitral flow with low velocity.

An alternative explanation for prolongation of t/2 in patients with aortic regurgitation is that the increase in left ventricular end diastolic pressure impedes left atrial emptying. The relation between t/2 and end diastolic pressure in our patients, however, was less obvious than that between t/2 and aortic regurgitation grade, and t/2 was normal in patients with raised end diastolic pressures due to congestive heart failure of non-valvar origin.

In conclusion, non-invasive grading of aortic regurgitation by measurement of mitral flow impairment with a simple continuous wave Doppler ultrasound method without simultaneous imaging is feasible in patients without concomitant mitral valve disease.

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*Br Heart J* 1986, 55: 286–90

# Comparative aspects of the dual role of the human atrioventricular node

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SUMMARY As well as transmitting the impulse from the atria to the ventricles the atrioventricular node has two other important functions namely: (*a*) synchronisation of atrial and ventricular contractions by a varying delay; and (*b*) protection of the ventricles from rapid atrial arrhythmias. The relative importance of these two functions appears to differ in large and small mammalian hearts. In small mammals synchronisation of atrial and ventricular contractions is the major function of the atrioventricular node, whereas protection from rapid atrial arrhythmias may be its most important function in large mammals. Atrioventricular conduction time in sinus rhythm is ten times longer in the whale (500 ms) than in the rat (50 ms). A whale heart, however, is about 100 000 times heavier than a rat heart. During atrial fibrillation the ventricular rate in a dog heart is only three times faster than in a horse, whereas a horse heart may be 40 times as heavy as that of a dog. Hence there is a considerable discrepancy between the size of the mammalian heart and the functions of its atrioventricular node. Analysis of several anatomical and functional aspects of atrioventricular conduction systems in mammals of all sizes showed that the importance of the delaying role of the atrioventricular conduction system diminishes as the size of the mammal increases, whereas the protective role of the atrioventricular node probably increases. The function of the human atrioventricular node seems to be intermediate between that of the small and large mammals.

In normal hearts electrical impulses travelling from the atria to the ventricles have to traverse the atrioventricular node. "The relation between heart size and the time intervals of the heartbeat with particular reference to the elephant and the whale" was reported by White and his associates almost 70 years ago.[1-3] They stressed the essential role of the atrioventricular conduction system in determining the PR interval and QRS duration.[4] Traditionally the atrioventricular node is regarded as the delay and synchronisation centre between atrial and ventricular contractions.[5 6] Precise tuning of atrioventricular delay optimises the contribution of atrial contraction to ventricular filling and subsequent contraction. Such adjustments allow some human beings to run the 100 m within 10 seconds or to cover the marathon in less than 2½ hours.

Patients with the Wolff-Parkinson-White syndrome have an accessory pathway directly connecting the atria and the ventricles. This connection lacks the protective delay of the normal atrioventricular node.[7 8] The electrophysiological properties of the accessory atrioventricular pathway, for example a short refractory period or a limited capacity for concealed conduction or both,[9-13] result in a bypass or short circuit of the normal atrioventricular connection.

Because they lack normal atrioventricular nodal delay such patients are more susceptible to ventricular tachycardia or even ventricular fibrillation in the presence of rapid atrial arrhythmias such as atrial fibrillation.

Thus, in addition to its potential to act as an emergency pacemaker, the human atrioventricular node has two equally important functions: (*a*) a synchronisation of atrial and ventricular contractions by a varying delay; and (*b*) protection of the ventricles from atrial tachycardias. A comparative analysis of this dual atrioventricular nodal role in various mam-

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Accepted for publication 19 November 1985

malian hearts may help us to a better understanding of atrioventricular conduction in human beings under normal and abnormal conditions.

## COMPARATIVE MORPHOLOGY

All mammalian hearts have essentially the same architecture. A knowledge of the anatomy of the heart of one species usually makes recognition of corresponding anatomical details in other mammalian hearts easy. Nature has used the same blueprint for all mammalian hearts from the mouse to the whale.[14]

In addition there are considerably more similarities than differences between the ultrastructure of cardiac muscle in different mammals, for example the presence of transverse tubules in mammalian myocardial fibres.[15 16] Moreover, cardiac muscle cells tend to be of uniform diameter (approximately 10 to 15 $\mu$m).[16-18] The diameter of mammalian myocardial fibres reflects an optimal relation between cell volume and the oxygen diffusion rate.[19] Furthermore, there is little difference in metabolic rate per gram tissue between the rabbit and elephant.[20] Hence, not only do the blueprints of all mammalian hearts show great similarities, but the bricks with which the mammalian hearts are built are of similar size and form.

Despite the great anatomical similarities in the mammalian atrioventricular conduction systems,[21 22] there are geometrical and morphological differences as well.[23 24] For instance, the so called classic, large Purkinje cells of the heart are found mainly in the larger mammals like ungulates, elephants, and whales. In small mammals the special conduction fibres can be identified only by the absence of transverse tubules.[16 24] In human hearts the distribution of Purkinje cells seems to be related to maturity and heart size. In infants and children it is rare to find Purkinje cells in the bundle branches.[25]

## HEART WEIGHT IN MAMMALS OF DIFFERENT SIZES

Heart weight varies nearly as the first power (0·98) of body weight over essentially the whole mammalian range.[26] The weight of the mammalian heart is about 0·6% of the body weight.[27] From comparative anatomical studies[21 22 24] it appears that the size (volume would be a better word) of the atrioventricular mammalian node also increases with the size of the heart, although not in a fully proportional manner. The heart of a 30 ton whale weighs approximately 100 000 times as much as the heart of a 300 g rat and one would expect that the whale's atrioventricular node would also be about 100 000 times larger than that of a rat. In terms of length rather than volume or weight the atrioventricular node of the whale will be 40–50 times greater than that of the rat. These considerable differences in size of the atrioventricular node are not reflected in the functions of the atrioventricular conduction system.[28]

## COMPARATIVE FUNCTION

Atrioventricular conduction time in the rat is about 40–50 ms while even in the largest whales it is probably not more than 500 ms.[28 29] Heart rate in a large whale is 6–10 beats per minute except when the animal is diving,[30] and in the rat it is 300–360 beats per minute.

The postulated scaling factor between the whale and the rat for the estimated volume of the atrioventricular node is 100 000, but the ratio of atrioventricular conduction times is only 10. Thus there is a 10 000 fold mismatch between size and function. There is a similar discrepancy between dimensions of the heart and function in QRS duration, which is 150–200 ms in the elephant or whale and 10–20 ms in the rat.[29] In 1927 Clark observed that "The most striking thing is, that the P–R interval varies so little in different animals. The delay at the a.–v. junction therefore varies relatively little in different species of mammals."[28]

## ATRIAL FIBRILLATION

Since all mammalian myocardial cells are approximately the same size, the hearts of large mammals must contain very many more cells than small hearts.[17] As early as 1914 Garrey,[31] and more recently Moe and his group,[32 33] showed that large hearts are more vulnerable to fibrillation than small hearts. In fact the rat heart rarely if ever fibrillates.[34] Atrial fibrillation would be expected to occur quite often in large mammals, and this is certainly borne out by findings in horses.[35]

Possibly because the organisation of atrial and ventricular electrical excitation differs[36 37] atrial fibrillation is much more common than ventricular fibrillation.

The magnitude of differences between ventricular rate and rhythm during atrial fibrillation in dog, man, and horse is remarkably small considering their great differences in heart size.[38] For instance, the median ventricular rate during atrial fibrillation in the horse is 50–60 beats per minute compared with 150–180 beats per minute in the dog. Thus during atrial fibrillation the horse heart beats only three times more slowly although it is at least 40 times larger. Neither the anatomical nor the physiological basis for this relatively small difference in ventricular rate is known. It is unlikely to be due to differences in the nature of atrial fibrillation itself, since few morphological and electrophysiological differences have been seen between different types of mammalian atrial cells.[15 39] Possibly the atrioventricular nodes of larger mammals contain fewer cells per given volume of node.[22]

### ATRIOVENTRICULAR CONDUCTION VELOCITY

Despite the considerable difference in the size of their hearts there is little difference between the atrioventricular conduction times of, for example, the horse and the whale.[29] The same is true for the PR interval in relation to age (and thus heart size) in man—this ranges from 100–110 ms in the neonate to only 150–200 ms in the adult.[40] It is also striking that the timing of the atrial contraction relative to the ventricular contraction appears to be fairly constant in larger hearts—for example those of the horse, elephant, and whale. Moreover, I have observed that in the elephant, for instance, there is little change in PR duration with heart rate; this accords with data presented by White *et al.*[2]

Given that diastole lasts longer in large mammals, the duration of the PR interval may have less influence on efficient ventricular ejection in larger animals. The importance of the role of the atrioventricular node for tuning atrioventricular delay seems to diminish as the size of the heart increases.

Since the size and arrangement of Purkinje fibres within the His bundle are very similar in sheep and whales[16] such features cannot explain why the PR interval in the whale is only twice as long as that in the sheep. Similar fibre diameter in the His bundles should result in similar conduction velocities[41 42]; however, Pressler[43] and others[44 45] reported a disparity between conduction velocity and fibre diameter. Sommer and Johnson believe that an increase in the diameter of the conduction fibres from approximately 10 $\mu$m in the small mammal to around 50 $\mu$m in the hearts of large mammals can explain the faster conduction in large mammals.[15]

Conduction velocity may also increase within the Purkinje fibres as the size of the animal increases. Unfortunately the data that are most relevant to these assertions—that is those from the mouse, elephant, and whale—are not available. The arrangement of the fibres within the bundles and intercellular resistance may also affect conduction velocity.

The conduction velocity in the large branches of the human heart is about 2·5 m/s.[46] In a large whale the His bundles are probably about one metre long. To obtain PR intervals of 500 ms (or less), at the same atrioventricular nodal delay, conduction velocity within the His bundles of a large whale would have to be 20–40 times faster than in the human heart. This seems highly unlikely. Assuming a more or less similar conduction velocity in the whale's His bundles as in those of the human heart, it would take several hundred ms to cover the distance from atrioventricular node to the intramyocardial Purkinje network. If this assumption is true, the atrioventricular node in a whale's heart is unlikely to contribute much to the total PR interval.[28]

## Discussion

The preceding arguments suggest that impulse delay and synchronisation in the atrioventricular node may not be important in very large mammals such as the elephant and whale. In such animals the atrioventricular node can make little or no contribution to atrioventricular conduction delay because propagation through the His bundle(s) itself must account for most of the atrioventricular conduction time. Nevertheless, the atrioventricular node remains important in larger mammals. Large mammals, such as human beings and horses, particularly older ones, often develop atrial fibrillation.[37 47–49] The major importance of the atrioventricular node in large mammals may well be the protection of the ventricles against fibrillation or tachycardias during atrial fibrillation or other rapid atrial arrhythmias.

The human body is near the median of the logarithmic mammalian weight scale; in terms of atrioventricular node function it also occupies an intermediate position. In the young the atrioventricular node beautifully synchronises atrial and ventricular contractions, so that strenuous exercise may be performed. In old age the function of the atrioventricular node in protecting the individual against arrhythmias becomes crucial to survival. The dual role of the atrioventricular node in the human heart represents a watershed between atrioventricular nodal function in the small and the large mammalian species.

This paper is the result of lengthy discussions with and the constructive criticism of many friends and colleagues.

Supported by the Wijnand M Pon Foundation, Leusden, The Netherlands.

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# Treatment of paroxysmal supraventricular tachycardia with intravenous injection of adenosine triphosphate

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SUMMARY Intravenous adenosine triphosphate rapidly terminated all 11 episodes of paroxysmal supraventricular tachycardia in 10 patients. Eight patients reported side effects but these resolved within 20 seconds and did not require treatment.

Adenosine triphosphate is a suitable agent for the rapid termination of paroxysmal supraventricular tachycardia.

Verapamil, propranolol, digitalis, and cardioversion have all been used to treat paroxysmal supraventricular tachycardia. Since 1955 adenosine triphosphate has also been used in some parts of Europe to treat acute episodes of paroxysmal supraventricular tachycardia, and the electrophysiological effects of this agent have been reviewed by Belhassen and Pelleg.[1] The effect of adenosine triphosphate on the sinus and atrioventricular nodes has been investigated in animals.[2 3] The effects of adenosine triphosphate are largely mediated by its metabolite, adenosine. Adenosine, which is increased in the ischaemic myocardium, has been implicated in the causation of atrioventricular block.[4 5] DiMarco *et al* reported that intravenous adenosine depressed sinus node automaticity and atrioventricular conduction and was an effective agent in the treatment of re-entrant supraventricular arrhythmias.[6] More recently the effect of adenosine on atrioventricular conduction has been attributed to its binding to extracellular receptors.[7] Adenosine, like acetylcholine, has been reported to increase potassium conductance,[8] to reduce calcium mediated slow channel influx,[9] and possibly to have indirect antiadrenergic effects.[10] Adenosine triphosphate in dogs had direct negative dromotropic and chronotropic effects (not involving a cholinergic component) which lasted for 5–30 seconds, and repeated administration produced neither tolerance nor cumulative effects.[3] The purpose of the present study was to determine the efficacy, rapidity of action, and side effects of adenosine triphosphate in the treatment of paroxysmal supraventricular tachycardia.

## Patients and methods

We studied 11 episodes of tachycardia in 10 patients (6 men and 4 women, mean (SD) age 56 (15) years). Table 1 shows the clinical characteristics of the patients. Five patients had been treated over several years at intervals of 1–9 months. One patient (case 4) had sick sinus syndrome with bradycardia-tachycardia syndrome. Another had isolated Wolff-Parkinson-White syndrome, and none had congestive heart failure. During the episodes of tachycardia all patients complained of palpitation, two complained of mild dyspnoea, and two complained of cold sweats.

### FEATURES OF TACHYCARDIA

The heart rate ranged from 146 to 200 beats per minute, and in each patient the rate was constant from minute to minute. The P wave was not seen in 8 (73%) episodes; it apparently occurred simultaneously with the QRS complex. The P wave was confined to the proximal portion of the ST segment in two patients so that the R–P′ interval was shorter than the P′–R interval. One patient (case 3) had longer R–P′ intervals than P′–R intervals, suggesting a fast-slow form of junctional re-entrant tachy-

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Accepted for publication 30 September 1985

Table 1 *Clinical characteristics of patients with paroxysmal supraventricular tachycardia*

| | *Age (yr)* | *Heart rate (beat/min)* | *Blood pressure (kPa)* | | *Interval from beginning of attack to treatment (h)* |
|---|---|---|---|---|---|
| | | | *Systole* | *Diastole* | |
| Mean | 56 | 168 | 12·57 | NA | 2·6 |
| Range | 28–76 | 146–200 | 7 71–15 96 | Undetectably low—13·30 | 0 2–5 0 |

Because diastolic blood pressure was undetectably low in four episodes, mean values of diastolic pressure were not calculated.
Conversion: SI to traditional units—1 kPa = 7 5 mm Hg

cardia.[11] The QRS configuration was identical to that of sinus rhythm except in the patient with Wolff-Parkinson-White syndrome in whom the duration of the QRS complex was normal during tachycardia.

### STUDY PROTOCOL

After we had measured blood pressure and had obtained a standard 12 lead electrocardiogram, we injected adenosine triphosphate intravenously as rapidly as possible (within 5 seconds). Eight attacks in eight patients were treated with 20 mg and three attacks in two patients were treated with 10 mg. Lead II or CM5 electrocardiograms were continuously recorded from just before the injection to one minute after the end of tachycardia or until two minutes after the end of adenosine triphosphate injection, and the electrocardiogram was then monitored for the next five minutes. We noted the interval between adenosine triphosphate injection and the end of tachycardia, the pause at termination, the pattern of interruption, side effects, and blood pressure three minutes after termination.

## Results

Five episodes of tachycardia were treated with adenosine triphosphate within two hours and six episodes were treated between three and five hours after the beginning of the episode. Systolic blood pressure before treatment varied from 7·71 to 15 96 kPa (58 to 120 mm Hg). In three cases (four episodes) diastolic blood pressure was too low to measure with a sphygmomanometer.

The Figure shows a typical response on the electrocardiogram (lead CM5) to 20 mg of adenosine triphosphate (case 10). The heart rate during tachycardia was 160 beats/minute. The tachycardia ended 6·2 seconds after injection of the nucleotide, and this was followed by sinus rhythm with wide QRS complex and pronounced atrioventricular block. Regular sinus rhythm was restored 14·4 seconds after the end of tachycardia, after an intervening period of atrioventricular dissociation. The patient complained of mild nausea which disappeared within 10 seconds.

All patients responded well to adenosine triphosphate. In the patient with sick sinus syndrome, however, a second episode of supraventricular tachycardia started five minutes after the end of the first episode. On two separate occasions a patient with Wolff-Parkinson-White syndrome was successfully treated with adenosine triphosphate. Table 2 summarises the effects of the nucleotide on the electrocardiograms obtained during the 11 episodes. Tachycardia ended within 15 seconds (mean 10 7 (3·4)) of the start of the injection of adenosine triphosphate. The first QRS complex appeared within four seconds of the end of tachycardia in 10 episodes; the remaining episode was followed by a pause lasting for approximately six seconds. The first QRS complex originated from the sinus node after six episodes, from the atrioventricular junction after four episodes, and from the ventricle after one episode. The longest R-R interval occurred between the first and the second heart beat or between the second and the third heart beat in six episodes, and after two episodes the longest R-R interval occurred immediately after the end of tachycardia. Sinus arrest or pronounced sinus bradycardia and atrioventricular block with junctional escape beats were common features at the end of tachycardia. Regular sinus rhythm was restored within 18 seconds of the end of tachycardia. No ventricular arrhythmias were precipitated. Blood pressure measured three minutes after the end of tachycardia was significantly higher than during tachycardia.

### SIDE EFFECTS

Eight patients reported side effects, but these resolved within 20 seconds and required no action.

## Discussion

All 11 episodes of paroxysmal supraventricular tachycardia in 10 patients responded successfully to treatment with intravenous injection of adenosine triphosphate. Digitalis, beta blockers, and cardioversion have all been used for the short term treatment of paroxysmal supraventricular tachycardia, but intravenous verapamil is the current drug of

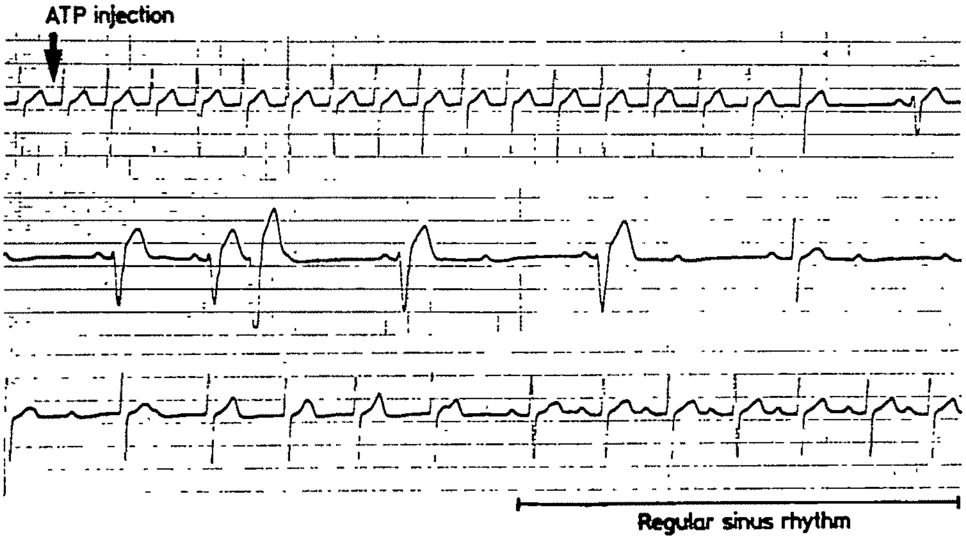

Fig *Electrocardiogram from lead CM5 in case 10. Three continuous sections of the record are shown. Paroxysmal supraventricular tachycardia ended 6·2 seconds after injection of adenosine triphosphate (20 mg), and 14·4 seconds later regular sinus rhythm (100 beats/min) was restored.*

choice. Verapamil is reported to be successful in most patients,[12 13] but it can cause hypotension or bradycardia and aggravate heart failure, especially in patients with myocardial disease[14] or in those who have been treated with beta blockers.[15] The half life of intravenous verapamil has been estimated to be 18–45 minutes in the initial rapid phase (α phase) and 3–6 hours in the later slow period (β phase),[16 17] and persistence of the active drug in the plasma may complicate the management of patients with side effects. A comparative study of adenosine and adenosine triphosphate in the dog showed that the nucleotide produced direct negative dromotropic and chronotropic effects on atrioventricular conduction and on atrioventricular junctional rhythm respectively.[3] DiMarco *et al* also reported a remarkable effect of adenosine for short term treatment of supraventricular tachycardia whenever re-entry through the atrioventricular node is involved.[18] These effects strongly suggest that adenosine triphosphate may be effective in terminating acute episodes of supraventricular tachycardia that affect the atrioventricular node via the re-entry pathway. Previous reports had suggested that the actions of adenosine triphosphate on tachycardia are due to adenosine produced by hydrolysis of the nucleotide.[3 6]

Table 2 *Timing of electrocardiographic events after injection of adenosine triphosphate*

| *Case No* | *ATP dose (mg)* | *I to end time (s)* | *End to P time (s)* | *End to R time (s)* | *Longest R–R interval (s)** | *End to sinus time (s)* |
|---|---|---|---|---|---|---|
| 1 | 10 | 10·8 | 1·8 | 2·1 | 1·8 | 7·1 |
| 2 | 10 | 12·0 | 2·6 | 2·8 | 3·2 | 11·2 |
| 3a | 10 | 8·4 | 1·0 | 1·2 | 1·4 | 2·1 |
| 3b | 20 | 10·0 | 8·5 | 1·3 | 3·2 | 10·0 |
| 4 | 20 | 15·0 | 3·0 | 3·2 | 3·2 | 14·0 |
| 5 | 20 | 12·0 | 6·0 | 1·8 | 2·8 | 6·2 |
| 6 | 20 | 8·0 | 2·0 | 2·5 | 6·0 | 10·4 |
| 7 | 20 | 10·0 | 1·7 | 0·5 | 2·3 | 11·0 |
| 8 | 20 | 7·4 | 3·6 | 2·1 | 2·0 | 8·5 |
| 9 | 20 | 14·4 | 10·0 | 6·0 | 10·0 | 15·0 |
| 10 | 20 | 6·2 | 0·8 | 1·0 | 1·7 | 14·4 |
| Mean | | 10·7 | 3·7 | 2·2 | 3·4 | 10·0 |
| SD | | 3·4 | 3·1 | 1·5 | 2·5 | 3·9 |

ATP, adenosine triphosphate; I to end time, interval from injection of adenosine triphosphate to end of tachycardia, end to P time, time from end of tachycardia to the first P wave after termination of tachycardia, end to R time, time from end of tachycardia to the first QRS complex after end of tachycardia; end to sinus time, time from end of tachycardia to restoration of regular sinus rhythm; SD, standard deviation

*Longest R–R interval after end of tachycardia.

Ronca-Testoni and Borghini have shown that adenosine triphosphate is almost completely metabolised to adenosine during a single passage across the heart, and adenosine[19] is only effective for 30 seconds because it is so rapidly taken up by most types of cell and deaminated to inosine which is inactive. The rapid clearance of adenosine triphosphate from plasma means that tachycardia may be safely treated by monitoring the response to a given dose over only one or two minutes, and then gradually increasing the dose until the arrhythmia stops. Repeated doses, even when these are increased, are not cumulative, and the side effects disappear within seconds. This characteristic is the main advantage of adenosine triphosphate, which did not cause harmful side effects and is unlikely to interact in an unpredictable way with other drugs or cardioversion.

We used 10 mg or 20 mg doses of adenosine triphosphate in this study. Greco *et al* used 15 mg of adenosine triphosphate to treat episodes of tachycardia in infancy.[20] In adults, Somlo,[21] Komor and Garas,[22] Coumel *et al*,[23] and Motte and his coworkers[24] have reported considerable success after single doses of 10–70 mg of the nucleotide without harmful side effects. In the present study 10 mg of adenosine triphosphate successfully converted tachycardia to sinus rhythm in all three cases in which it was used. This result suggests that, in Japanese patients at least, doses of the nucleotide should start at 10 mg or less with a gradual increase in dose every two or three minutes until the tachycardia is terminated.

In conclusion, adenosine triphosphate has features that indicate that it may be one of the safest and the most effective methods of treating paroxysmal supraventricular tachycardia, but more extensive trials are needed to establish this.

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# Socioeconomic factors and physical activity in relation to cardiovascular disease and death

## *A 12 year follow up of participants in a population study of women in Gothenburg, Sweden*

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SUMMARY In a prospective population study of middle aged women socioeconomic factors and physical activity as initially reported were related to the 12 year incidence of ischaemic heart disease and to total mortality. There was a significant age specific correlation between low socioeconomic status according to the husband's occupation and myocardial infarction. No such association was seen between the socioeconomic status of the women themselves and myocardial infarction. Women with a low educational level had a significantly increased age specific incidence of angina pectoris. There was no significant correlation between marital status or number of children and incidence of ischaemic heart disease or overall mortality. Women who initially reported low physical activity at work during the last year had a significantly increased age specific 12 year incidence of stroke and death, as did those who reported low physical activity during leisure hours in whom the incidence of myocardial infarction and electrocardiographic changes indicating ischaemic heart disease were also increased. Multivariate analyses showed that the association between low educational level and incidence of angina pectoris was independent of socioeconomic group, smoking habits, systolic blood pressure, indices of obesity, serum triglycerides, and serum cholesterol. Similarly, low physical activity during leisure hours seemed to be an independent risk factor for stroke, and low physical activity at work was an independent risk factor for overall mortality.

Socioeconomic factors and lifestyle, with the exception of smoking habits, have not attracted the same degree of interest as traditionally accepted risk factors, such as arterial hypertension and hyperlipidaemia, in studies of risk factors for ischaemic heart disease. Education,[1 2] marital status,[2 3] number of children,[2 4 5] socioeconomic status,[5 6] and degree of physical activity[4 7] have been reported to be related to cardiovascular disease in women. Some of the observations mentioned were made in a case control study carried out by our group.[4] We considered it important to re-evaluate our cross sectional results in a prospective study.

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Accepted for publication 4 November 1985

## Study population

A population study of 1462 women aged 38, 46, 50, 54, and 60 was carried out in Gothenburg, Sweden, in 1968–69.[8] The systematic sampling method, based on date of birth, and a high participation rate (90·1%), ensured that the participants were a representative cross section of women from the community studied. Table 1 shows the number of participants in the initial examination.

The population sample was followed up in 1974–75 and in 1980–81. Of those participating in 1968–69, 1154 (78·9%) took part in the 1980–81 follow up. Most of the non-participants in these follow up studies were interviewed by telephone or letter about their history of angina pectoris, myocardial infarction, or stroke. Hence information was

Table 1 *Participants and participation rates in the population study of women in Gothenburg 1968–69*

| *Age (yr)* | *Participants (No)* | *Participation rate (%)* |
|---|---|---|
| 38 | 372 | 91·4 |
| 46 | 431 | 90·0 |
| 50 | 398 | 91·3 |
| 54 | 180 | 88·7 |
| 60 | 81 | 83·5 |
| *Total* | 1462 | 90·1 |

obtained from a total of 1351 women (97·4% of those participating in 1968–69 and still alive in 1980–81). Further details of the studies in 1968–69, 1974–75, and 1980–81 have been presented elsewhere.[8–10]

## Methods

### COLLECTION OF SOCIAL DATA

Information on place of birth of the women participating in the population study was obtained from the Revenue Office Register.[4] Information about education, marital status, number of children, and socioeconomic status was obtained by a questionnaire.[4] The subjects were divided into five socioeconomic groups according to Carlsson.[11] Group 1 according to this classification is group I in the present paper (large-scale employers and officials of high or intermediate rank), groups 2 and 3 are group II (small-scale employers, officials of lower rank, foremen), and groups 4 and 5 are group III (skilled and unskilled workers). Housewives were classed as a separate group.

### INTERVIEW ABOUT PHYSICAL ACTIVITY

The subjects were interviewed about their physical activity at work and during leisure hours. On the basis of the level of physical activity we assigned women to groups I–IV, using a classification which had previously been used for men in Gothenburg[12] and modified for women.[4] For example, women with light office work and no domestic work were assigned to group I for physical activity at work; women with shop work, light industrial work, or domestic work including the care of one child to group II; women with hospital work or domestic work including the care of two or three children to group III; and those with heavy work together with domestic work, or just domestic work including the care of four or more children to group IV. As regards activity during leisure hours, examples of group I activities are reading or looking at television, group II walking or cycling for half an hour a day, group III regular exercise such as running, tennis, or swimming, and group IV heavy exercise or competitive sports.

### CLINICAL EXAMINATION

In the initial study of 1968–69, blood samples were taken after an overnight fast.[4] Body weight was measured to the nearest 0·1 kg with a balance scale. Body height without shoes was measured to the nearest 0·5 cm. Body mass index was calculated as weight/height$^2$ (kg/m$^2$). Waist and hip circumferences were measured and the waist : hip circumference ratio was calculated.[13] Blood pressure was measured with a mercury manometer in the seated position after about 5 minutes' rest.[4] Information about smoking habits was obtained by means of a standardised interview.[4]

### END POINTS DURING THE FOLLOW UP PERIOD

*Myocardial infarction*—Each participant was asked whether she had any history of chest pain, as were most of the non-participants in the follow up studies. Records of all women who were admitted to hospital because of chest pain were studied, and acute myocardial infarction was defined as the presence of at least two of the following symptoms: (*a*) central chest pain, (*b*) transient rise of transaminase activities, and (*c*) typical electrocardiographic changes of recent onset. These criteria have been described in detail elsewhere.[14] Fatal myocardial infarction was determined from the diagnosis on the death certificate. "Silent" myocardial infarction was defined as electrocardiographic changes interpreted as Minnesota code 1·1[15 16] without a history of myocardial infarction. In our analysis, we used the combined incidences of fatal and non-fatal myocardial infarction. The incidence of "silent" myocardial infarction was added only when indicated in the text.

*Angina pectoris*—During an interview, patients were asked whether they had a history of chest pain. A diagnosis of angina pectoris was accepted when the criteria proposed by Rose were fulfilled.[17]

*Electrocardiographic changes indicating ischaemic heart disease.*—Electrocardiography was performed on all participants during rest in 1968–69 and in 1980–81. Minnesota codes[15 16] 1·1–2, 4·1, 5·1–2 (in the absence of 3·1), 6·1, or 7·1 were taken to indicate ischaemic heart disease.

*Stroke* was defined as described by Harmsen and Tibblin.[18] If non-fatal, a hospital diagnosis was required. Stroke was also recorded for subjects who at necropsy showed signs consistent with a recent cerebrovascular accident and for subjects in whom stroke was recorded as the main cause of death on their death certificates.

*Death.*—At the end of 12 years we were able to establish the vital status of 1458 (99·7%) of the initial participants. Death certificates were obtained for all participants who died. Necropsies were performed in five patients dying of myocardial infarction and in 27 (40%) of 67 women in whom myocardial infarction had not been recorded on the death certificate. Patients with findings positive for myocardial infarction at the initial examination were excluded when the risk of myocardial infarction as an end point was assessed. Similarly, patients with findings positive for other end points at the initial examination were excluded in the final calculation for the corresponding end points.

### STATISTICAL METHODS

We used an extension of the $\chi^2$ procedure according

Table 2 *Observed and expected frequencies of end points in women born in the County of Gothenburg, women who had been living in Gothenburg for > 25 years, women born outside Scandinavia, and women who had grown up in a big city. 95% confidence interval for the age adjusted relative risk compared with other women is given in parentheses*

| *End points* | *Observed* | *Expected* | *Relative risk* |
|---|---|---|---|
| *Born in Gothenburg or its environs (n = 763)* | | | |
| Myocardial infarction | 15 | 12·8 | 1·5 (0·6–3·5) |
| Angina pectoris | 30 | 25·3 | 1·0 (0·6–1·7) |
| Electrocardiographic changes | 39 | 39·6 | 1·0 (0·6–1·6) |
| Stroke | 8 | 7·2 | 1·3 (0·4–4·1) |
| Death | 44 | 40·8 | 1·2 (0·7–2·0) |
| *Living in Gothenburg for > 25 years (n = 854)* | | | |
| Myocardial infarction | 18 | 15·8 | 1·8 (0·6–5·3) |
| Angina pectoris | 36 | 34·3 | 1·2 (0·6–2·1) |
| Electrocardiographic changes | 43 | 44·0 | 0·9 (0·6–1·6) |
| Stroke | 12 | 9·1 | 5·2 (0·9–29·8) |
| Death | 56 | 51·0 | 1·5 (0·9–2·6) |
| *Born outside Scandinavia (n = 44)* | | | |
| Myocardial infarction | 0 | 0·5 | — |
| Angina pectoris | 3 | 1·7 | 2·0 (0·6–6·8) |
| Electrocardiographic changes | 3 | 2·3 | 1·4 (0·4–4·6) |
| Stroke | 0 | 0·3 | — |
| Death | 0 | 1·6 | — |
| *Grown up in a big city (n = 689)* | | | |
| Myocardial infarction | 11 | 11·4 | 0·9 (0·4–2·2) |
| Angina pectoris | 28 | 26·6 | 1·1 (0·6–1·9) |
| Electrocardiographic changes | 31 | 34·1 | 0·8 (0·5–1·3) |
| Stroke | 9 | 6·4 | 2·4 (0·7–8·2) |
| Death | 42 | 36·2 | 1·4 (0·9–2·3) |

Table 3 *Observed and expected frequencies of end points in women who had low educational level (elementary school only), women who were divorced, women who were widowed, and women who had four children or more at the beginning of the follow up period. 95% confidence interval for the age adjusted relative risk compared with other women is given in parentheses*

| *End points* | *Observed* | *Expected* | *Relative risk* |
|---|---|---|---|
| *Elementary school only (n = 1013)* | | | |
| Myocardial infarction | 20 | 16·7 | 2·6 (0·8–8·7) |
| Angina pectoris | 48* | 39·3 | 2·6 (1·3–5·5) |
| Electrocardiographic changes | 52 | 50·6 | 1·1 (0·6–1·9) |
| Stroke | 11 | 9·5 | 2·0 (0·5–9·0) |
| Death | 55 | 53·3 | 1·1 (0·6–1·9) |
| *Divorced (n = 117)* | | | |
| Myocardial infarction | 0 | 1·8 | — |
| Angina pectoris | 5 | 4·4 | 1·3† (0·5–3·3) |
| Electrocardiographic changes | 4 | 5·7 | 0·6† (0·2–1·8) |
| Stroke | 1 | 1·0 | 1·6† (0·2–12·2) |
| Death | 9 | 6·0 | 1·7† (0·8–3·6) |
| *Widowed (n = 62)* | | | |
| Myocardial infarction | 3 | 1·6 | 1·8† (0·6–5·5) |
| Angina pectoris | 3 | 2·6 | 1·2† (0·4–3·9) |
| Electrocardiographic changes | 2 | 3·2 | 0·6† (0·1–2·4) |
| Stroke | 2 | 0·9 | 3·0† (0·6–13·5) |
| Death | 5 | 5·1 | 1·1† (0·4–2·8) |
| *Four children or more (n = 142)* | | | |
| Myocardial infarction | 4 | 2·2 | 2·1 (0·7–6·2) |
| Angina pectoris | 8 | 5·1 | 1·7 (0·8–3·6) |
| Electrocardiographic changes | 6 | 6·9 | 0·8 (0·4–2·0) |
| Stroke | 2 | 1·2 | 1·8 (0·4–7·9) |
| Death | 7 | 7·3 | 1·0 (0·4–2·1) |

*$p < 0·01$ compared with other women in the population sample.
†Compared with married women.

to Mantel-Haenszel with one degree of freedom for analysis of frequencies in morbidity and mortality.[19] This minimises the effect of age as a confounding factor. Relative risk (risk ratio) and confidence limits of relative risk were calculated according to the Mantel-Haenszel estimation.[19,20] Associations between graded or continuous variables were tested by means of Pitman's non-parametric permutation test.[21] When adjusting for confounding variables, we used an extension of Mantel-Haenszel's procedure for permutation testing.[19] Two-tailed tests were used and p values $<0{\cdot}05$ were considered to be significant.

## Results

### INCIDENCE OF MYOCARDIAL INFARCTION, ANGINA PECTORIS, ELECTROCARDIOGRAPHIC CHANGES INDICATING ISCHAEMIC HEART DISEASE, STROKE, AND MORTALITY

Of all women initially free from signs of myocardial infarction from whom we obtained valid follow up data (n = 1424), 23 (1·6%) developed myocardial infarction during the follow up period (8 fatal myocardial infarction and 15 non-fatal myocardial infarction). Another five women developed "silent" myocardial infarction during follow up. New symptoms of angina pectoris were recorded in 56 (4·0%) of 1416 women, new electrocardiographic changes indicating ischaemic heart disease in 73 (6·0%) of 1218 women, and new signs of stroke in 13 (0·9%) of 1426 women. Altogether 75 women (5·1%) died during the follow up period.

### INITIAL SOCIOECONOMIC FACTORS IN RELATION TO END POINTS

*Myocardial infarction.*—Age specific 12 year incidence of myocardial infarction was significantly higher in the group of women who were initially assigned to socioeconomic group III according to their husbands' occupations than in other women ($p<0{\cdot}01$). There were no significant differences with respect to myocardial infarction when women who were born in Gothenburg or its environs, who had been living in Gothenburg for >25 years, who were born outside Scandinavia, who had grown up in a big city, who had a low educational level, who were divorced or widowed, who had four children or more, who were housewives or who were assigned to socioeconomic group III according to their own occupations were compared with other women (Tables 2, 3, and 4). Similar results were obtained when women with "silent" myocardial infarction were included.

*Angina pectoris.*—Women with a low educational level had a significantly increased age specific incidence of angina pectoris compared with other women ($p<0{\cdot}01$), but no other significant differences were seen when we studied the same socioeconomic factors as we did for myocardial infarction (Tables 2, 3, and 4).

*Electrocardiographic changes indicating ischaemic heart disease.*—No significant differences were observed (Tables 2, 3, and 4).

*Stroke.*—No significant differences were observed (Tables 2, 3, and 4).

*Mortality.*—No significant differences were found for variables included in Tables 2, 3, and 4.

Table 4 *Observed and expected frequencies of end points in women classified as housewives, women assigned to socioeconomic group III according to their occupation, and women whose husbands were assigned to socioeconomic group III. 95% confidence interval for the age adjusted relative risk compared with other women is given in parentheses*

| *End points* | *Observed* | *Expected* | *Relative risk* |
|---|---|---|---|
| | *Housewives (n = 498)* | | |
| Myocardial infarction | 6 | 8·3 | 0·8 (0·3–2·3) |
| Angina pectoris | 19 | 20·4 | 0·9 (0·5–1·6) |
| Electrocardiographic changes | 24 | 25·7 | 0·9 (0·6–1·5) |
| Stroke | 2 | 4·9 | 0·5 (0·1–2·5) |
| Death | 17 | 26·3 | 0·7 (0·4–1·3) |
| | *Socioeconomic group III according to the woman's occupation (n = 400)* | | |
| Myocardial infarction | 7 | 6·0 | 1·7 (0·5–5·6) |
| Angina pectoris | 15 | 15·4 | 0·9 (0·5–1·8) |
| Electrocardiographic changes | 19 | 20·2 | 0·8 (0·5–1·5) |
| Stroke | 5 | 3·6 | 5·4 (0·8–38·4) |
| Death | 21 | 20·3 | 1·3 (0·7–2·4) |
| | *Socioeconomic group III according to the husband's occupation (n = 487)* | | |
| Myocardial infarction | 14* | 7·9 | 4·6 (1·7–12·8) |
| Angina pectoris | 18 | 16·5 | 1·2 (0·6–2·2) |
| Electrocardiographic changes | 26 | 24·7 | 1·3 (0·7–2·2) |
| Stroke | 3 | 2·7 | 0·9 (0·2–4·0) |
| Death | 22 | 23·6 | 0·8 (0·5–1·5) |

*$p<0{\cdot}01$ compared with other women in the population sample

Table 5 *P values for age specific correlations between the end point and educational level, number of children, socioeconomic group according to the woman's occupation and according to the husband's occupation, and physical activity at work and during leisure hours*

| *Attributes* | *MI* | *AP* | *Electrocardiographic changes* | *Stroke* | *Mortality* |
|---|---|---|---|---|---|
| Educational level | NS | <0·01* | NS | NS | NS |
| Number of children | NS | NS | NS | NS | NS |
| Socioeconomic group according to the woman's occupation | NS | NS | NS | NS | NS |
| Socioeconomic group according to the husband's occupation | <0·05† | NS | NS | NS | NS |
| Physical activity at work | | | | | |
| For ages 20–38 | NS | NS | NS | NS | NS |
| After age 38 | NS | NS | NS | NS | NS |
| In past year | NS | NS | NS | <0·05* | <0·05* |
| Physical activity during leisure hours | | | | | |
| For ages 20–38 | NS | NS | NS | NS | NS |
| After age 38 | NS | NS | NS | NS | NS |
| In past year | NS | NS | NS | <0·01* | <0·05* |

*Negative correlation.
†Low socioeconomic group correlated with myocardial infarction (MI).
AP, angina pectoris

### MULTIVARIATE ANALYSIS

Table 5 shows the p values for the non-parametric correlations between educational level, number of children, socioeconomic group according to the women's own occupations and according to their husbands' occupations on the one hand and the end points myocardial infarction, angina pectoris, electrocardiographic changes indicating ischaemic heart disease, stroke, and mortality on the other, when age is taken into account as a background variable. Educational level was inversely correlated with angina pectoris ($p<0{\cdot}01$). In extended multivariate analyses the relation was independent of socioeconomic group and also independent of traditional risk factors for cardiovascular disease such as smoking habits, systolic blood pressure, indices of obesity, serum triglycerides, and serum cholesterol. When serum triglyceride concentration and waist : hip circumference ratio were included as potential confounding variables, the significance level changed from $p<0{\cdot}01$ to $p<0{\cdot}05$. The correlation between low socioeconomic group according to the husband's occupation and myocardial infarction was statistically significant ($p<0{\cdot}05$), but when the same background variables were included the correlation disappeared when serum triglyceride concentration, waist : hip circumference ratio, and body mass index were taken into account as background variables in multivariate analyses. No other significant correlations were observed (Table 5).

### INITIAL PHYSICAL ACTIVITY IN RELATION TO END POINTS

*Myocardial infarction.*—There was a significant age specific difference in the 12 year incidence of myocardial infarction in the group of women who had initially reported a low level of physical activity during leisure hours (group I) during the last year compared with other women ($p<0{\cdot}05$). No significant differences were observed when women who reported a low level of physical activity at work (group I) during the last year were compared with other women (Table 6). Similar results were obtained when women with "silent" myocardial infarction were included.

*Angina pectoris, electrocardiographic changes indicating ischaemic heart disease, and stroke.*—Increased age specific incidences of electrocardiographic changes indicating ischaemic heart disease ($p<0{\cdot}01$) and of stroke ($p<0{\cdot}001$) were seen in women who at the beginning of the follow up period reported a low level of physical activity during leisure hours (group I) in the past year. The incidence of stroke was also increased in the group of women who reported low physical activity at work (group I) in the past year ($p<0{\cdot}001$). There were no significant differences in the incidence of angina pectoris. Table 6 shows the results of the statistical analyses.

*Mortality.*—Women who initially reported low physical activity at work (group I) in the past year had an increased age specific mortality compared with other women ($p<0{\cdot}001$). Women who reported low physical activity during leisure hours (group I) in the past year also had an increased mortality when compared with other women ($p<0{\cdot}05$) (Table 6)

### MULTIVARIATE ANALYSIS

Table 5 shows the p values for the non-parametric correlations between initial physical activity at work and during leisure hours during the three life periods studied and the end points of myocardial

Table 6 *Observed and expected frequencies of end points in women initially assigned to activity group I for physical activity at work and during leisure hours in the past year. 95% confidence interval for the age adjusted relative risk compared with other women is given in parentheses*

| *End points* | *Observed* | *Expected* | *Relative risk* |
|---|---|---|---|
| | *Physical activity at work group I (n = 66)* | | |
| Myocardial infarction | 2 | 0·8 | 1 4 (0 3–6 7) |
| Angina pectoris | 2 | 2 4 | 0·8 (0 2–3·2) |
| Electrocardiographic changes | 1 | 3 0 | 0 3 (2·7–23 0) |
| Stroke | 4*** | 0 8 | 7·8 (2·7–23·0) |
| Death | 15*** | 4 8 | 5 2 (2 8–9 7) |
| | *Physical activity during leisure hours group I (n = 264)* | | |
| Myocardial infarction | 9* | 4 6 | 2·8 (1 2–6 5) |
| Angina pectoris | 10 | 10·1 | 1 0 (0·5–1·9) |
| Electrocardiographic changes | 22** | 13·5 | 2 0 (1·2–3·3) |
| Stroke | 9*** | 2·6 | 10 1 (3·8–27 1) |
| Death | 23* | 15 2 | 1·9 (1 1–3·2) |

*p < 0 05, **p < 0 01, ***p < 0 001 compared with other women in the population sample

infarction, angina pectoris, electrocardiographic changes indicating ischaemic heart disease, stroke, and mortality when age is taken into account as a background variable. Physical activity at work as well as physical activity during leisure hours during the past year and the incidence of stroke were negatively correlated ($p < 0{\cdot}05$ and $p < 0{\cdot}01$ respectively). When socioeconomic group, educational level, smoking habits, systolic blood pressure, indices of obesity, serum triglyceride concentration, and serum cholesterol concentration were included as potential confounding factors, physical inactivity during leisure hours during the last year was found to be independently correlated with stroke. The correlation between physical inactivity at work during the last year and the 12 year incidence of stroke was independent of all these background variables except for one of the indices of obesity (waist : hip circumference ratio). There was also a significant negative correlation between physical activity at work and physical activity during leisure hours during the past year and the 12 year mortality ($p < 0\ 05$). Multivariate analyses of the total mortality showed that low physical activity at work during the last year was an independent risk factor when all the potential confounding variables mentioned above were taken into account, but the inverse correlation between initial physical activity during leisure hours during the last year and total mortality disappeared when the waist : hip circumference ratio was included in the multivariate analyses. No other significant correlations were seen.

## Discussion

The information from previous prospective studies on socioeconomic factors and physical activity as risk factors for cardiovascular disease in women is limited. In a previous clinical study we compared all women who had myocardial infarction in the community during a three year period with women in our population sample of women who had been examined during the same period.[4] No significant differences in place of birth, educational level, marital status, or socioeconomic status were found between women with myocardial infarction and women in the general population. Physical inactivity, both at work and during leisure hours, was found to have been significantly more common during different periods of life in women who later had an acute myocardial infarction than in other women in the general population.

In the present prospective study, we found an independent correlation between low educational level and incidence of angina pectoris. As far as we know, such a correlation has not previously been reported. In two retrospective studies Szklo *et al* and Talbott *et al* found that women who had myocardial infarction or who had died suddenly showed more educational incongruity with their spouses than did those in a control population.[1 2]

Talbott *et al* found that women who died suddenly were less often married.[2] We did not find a significantly increased risk of cardiovascular disease or death among widows or any other civil status group either in our previous cross sectional study[4] or in this prospective study. In a prospective study of 2828 women Helsing and Szklo also found no increase in mortality risk for widows compared with married women.[22]

In our previous cross sectional study, we found that women with four or more children were overrepresented in the myocardial infarction group; similar results were reported from the Framingham study,[5] in which women working outside the home with three children or more had an increased risk of ischaemic heart disease. In a retrospective study, however, Talbott *et al* found that women who died suddenly had fewer children that those in the control population.[2] In our prospective study, we could not verify the increased risk found in our cross sectional study, but in our prospective study the risk ratio was doubled in women with four or more children.

In our prospective study socioeconomic status correlated with myocardial infarction only when classified according to the husband's occupation. The correlation with myocardial infarction disappeared when serum triglyceride concentration and indices of obesity were included as potential confounding variables in the multivariate analysis. Heller *et al* also studied the risk of ischaemic heart disease in women in relation to the occupation of their men and found that "women married to professional men are at a lower risk compared with other women."[6]

Physical inactivity was related to cardiovascular disease and death in the Framingham study[7] The investigators found an inverse correlation between physical activity and mortality due to cardiovascular disease but the statistical significance was lost when adjustment was made for age, probably because "the more sedentary women are older than the active ones." There was no significant correlation between physical activity and overall mortality in that study. We found an increased incidence of stroke and death in women who initially reported low physical activity at work and during leisure hours during the last year and, in addition, an increased incidence of myocardial infarction and electrocardiographic changes indicating ischaemic heart disease in women who reported low physical activity during leisure hours during the past year, even when age was considered as a background variable. When several potential confounding variables were included, physical inactivity at work was still a risk factor for mortality from all causes, and physical inactivity during leisure hours was an independent risk factor for stroke. These findings from our prospective study accord with those from our previous cross sectional study.[4] Low physical activity may be a causative factor. Another possibility might be that persons already disabled with latent ischaemic heart disease have a lower level of physical activity as well as an increased morbidity and mortality.

The causes of cardiovascular disease are still not explained. Traditionally accepted risk factors such as raised blood pressure, raised serum lipids, smoking habits, indices of obesity, and diabetes seem to explain only part of cardiovascular disease. Socioeconomic factors also seem to feature in the pathogenesis of cardiovascular disease.

The analyses and presentation of data were supported by grants from the Swedish Medical Research Council and the Faculty of Medicine of Gothenburg University.

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*Br Heart J* 1986; 55: 302–4

# *Case reports*

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# Dissecting aneurysm of the thoracic aorta presenting as right atrial obstruction

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SUMMARY A patient with a dissecting thoracic aortic aneurysm presented with acute low output cardiac failure due to right atrial obstruction. Five years earlier she had had her aortic valve replaced because of aortic regurgitation. Obstruction of the superior vena cava and pulmonary artery has been reported elsewhere as a complication of compression by thoracic aortic dissecting aneurysm. This case was unusual in presenting as right atrial obstruction.

Chronic non-dissecting thoracic aortic aneurysms may be complicated by rupture into or compression of adjacent vascular structures. Recorded vascular complications include aortocardiac fistula formation and fistula formation with or without compression of the superior vena cava and pulmonary artery.[1] Such complications with dissecting thoracic aneurysms, however, have been infrequent; this may be partly because most dissecting aneurysms are acute lesions.[2] We describe a case of dissecting thoracic aortic aneurysm that presented as compression of the right atrium.

## Case report

A 50 year old woman first presented in July 1979 with exertional dyspnoea. She had been treated for hypertension for the past 20 years. Examination showed signs of aortic incompetence, and her blood pressure was 200/75 mm Hg. Investigations confirmed severe aortic incompetence; there was no aortic valve pressure gradient, no evidence of mitral valve disease, and coronary angiography was normal. She underwent aortic valve replacement with a size 27 Björk-Shiley prosthesis. A standard cardiopulmonary bypass procedure was used with cross clamping of the aorta. The native valve had three cusps and histology showed dense collagenous fibrosis. Recovery after operation was uneventful.

During follow up she remained well, although antihypertensive medication had to be increased. Four years after valve replacement her chest radiograph, which had been satisfactory after operation, showed that the ascending aorta was dilated. She remained symptom free, the prosthetic valve sounds were satisfactory, and no cardiac murmurs were present.

In April 1985 she was admitted to hospital because for four days she had been breathless, weak, and tired but she did not have chest pain. She was pale, cold, and clammy with a respiratory rate of 50 per minute. Her pulse was 120 beats per minute and regular, systolic blood pressure was 50 mm Hg, and the jugular venous pressure was discernible 8 cm above the sternal angle. The prosthetic valve sounds were normal and there were no cardiac murmurs. The chest radiograph again showed a widened mediastinum and the lung fields were clear. Acute pulmonary embolism was suspected and the patient was transferred for further investigation.

On arrival at this hospital she had a profound metabolic acidosis (arterial pH 7·06). Echocardiography

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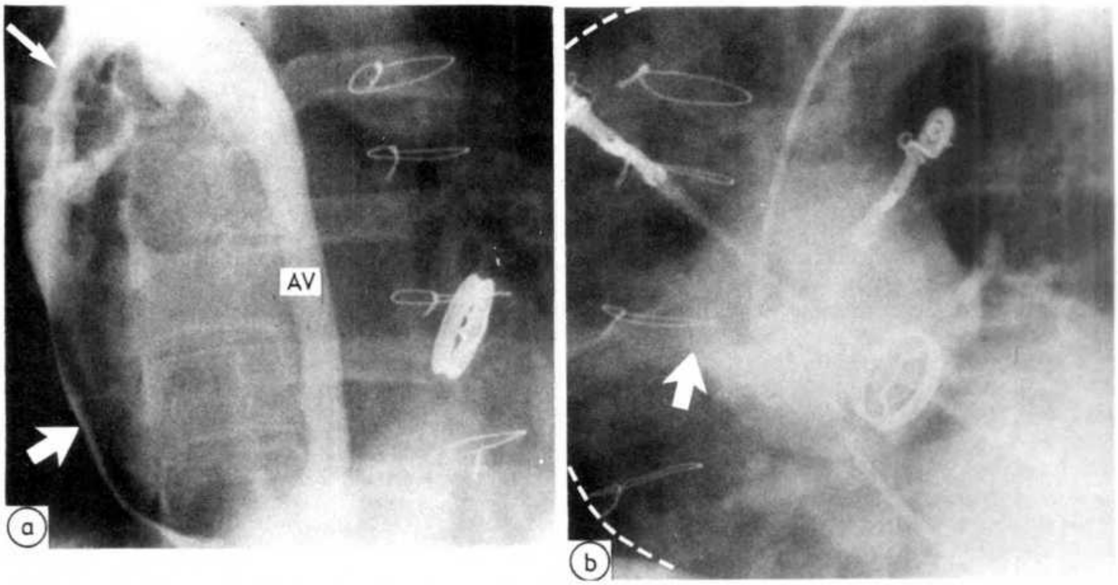

Fig. 1 *(a) Injection via catheter in superior vena cava (small arrow) with contrast in the right atrium (large arrow) and azygous vein (AV). There is a huge filling defect in the right atrium. An aortogram (b) shows a dilated ascending aorta and the entry point into the false lumen (arrow) whose limit is indicated (dotted line).*

was technically difficult and unhelpful. During right heart catheterisation it was difficult to manoeuvre the catheter in the right atrium. Injection of contrast into the superior vena cava showed a huge filling defect in the right atrium. Contrast flowed to the inferior vena cava via the azygous system and thence to the right atrium and right ventricle (Fig. 1a). Simultaneous recording of pressure in the superior vena cava and right ventricle showed a mean end diastolic pressure gradient of 10 mm Hg (Fig. 2).

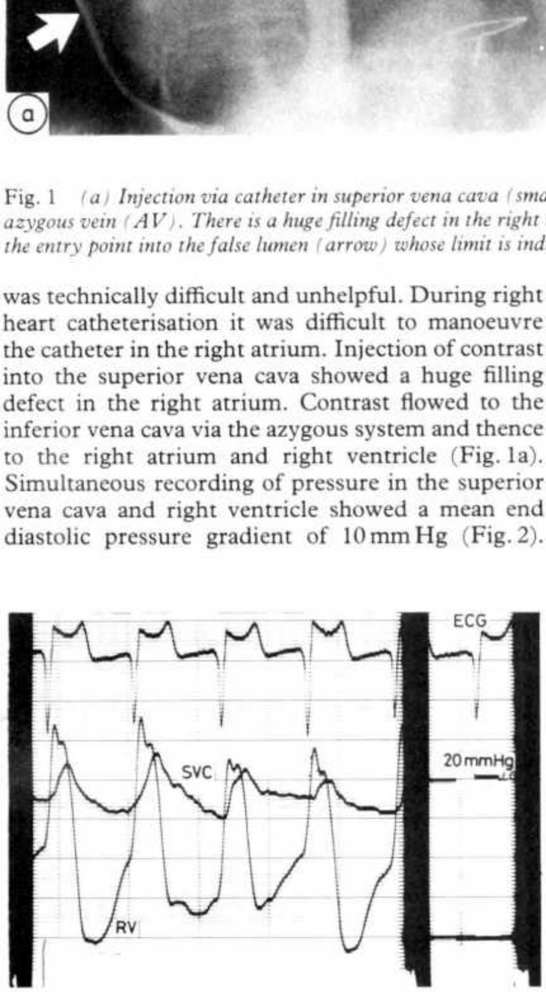

Fig. 2 *Simultaneous recording of superior vena cava (SVC) and right ventricular (RV) pressures showing an end diastolic gradient. ECG, electrocardiogram.*

Pulmonary arterial oxygen saturation was 59%, right atrial saturation was 57%, and aortic saturation was 93%. An aortogram showed gross dilatation of the ascending aorta. There was a dissection with the entry point 3–4 cm above the aortic valve. The false lumen was compressing the right atrium (Fig. 1b). Operation offered this patient the only possible chance of survival, and her clinical condition was poor.

At operation a massive ascending aortic aneurysm was found. The aneurysm was incised and the false lumen was entered. The old and new thrombus that it contained was removed. There was a tear in the right side of the ascending aorta 4 cm above and parallel to the previous valve suture line. The aneurysm had eroded the superior and medial walls of the right atrium; these were repaired and the ascending aorta was replaced by a woven Dacron graft. The patient required inotropic agents after operation and an intra-aortic balloon was subsequently inserted. She deteriorated progressively and died two days after operation.

## Discussion

The vascular complications of chronic non-dissecting thoracic aortic aneurysms include obstruction of the superior vena cava and pulmonary artery together with fistula formation with these structures and also aortocardiac fistulas. Reports of fistulous communications or compression of adjacent vascular structures by dissecting aneurysms, however, have been infrequent. One case of aorto-left atrial fistula[3] and four cases of aorto-right atrial fistula formation[4-7] associated with aortic dissection have been reported. Dissections may obstruct the superior vena cava and pulmonary artery as a result of extension of an intrapericardial haematoma; direct aneurysmal compression of these structures has also been described.[8-10] Morris and Barwinsky have suggested that when such vascular complications do occur they are the result of chronic rather than acute dissection.[11] We found no published reports of right atrial obstruction occurring as a complication of compression by a dissecting aneurysm of the thoracic aorta.

In this patient the cause of the aortic dissection and the sequence of events after aortic valve replacement remain uncertain. It seems likely that chronic aortic disease associated with longstanding hypertension resulted in progressive aortic dilatation, as confirmed on serial chest radiographs, and that this was eventually complicated by acute aortic dissection. Both aortic cannulation and cross clamping during cardiopulmonary bypass, however, may occasionally produce acute aortic dissection.[12 13] It is therefore possible that aortic dissection, which was not initially apparent radiologically, occurred after operation. A slow progressive enlargement of the false lumen could then explain the subsequent clinical and radiological course in this patient.

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*Br Heart J* 1986; 55: 305–7

# Left atrial rhabdomyosarcoma and the use of digital gated computed tomography in its diagnosis

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SUMMARY A case of left atrial rhabdomyosarcoma presenting in a patient with known mitral stenosis is described. Computed tomography of the left atrium, gated to the electrocardiogram cycle, was used to visualise the site and extension of the tumour.

With the exception of myxomata primary intracardiac tumours are rare. The presence or later appearance of an intracardiac tumour may be overlooked in a patient with rheumatic mitral valve disease.

We report a case of rhabdomyosarcoma of the left atrium in a patient with coincident mitral valve disease. We believe that this is the first such atrial tumour to be diagnosed with the help of gated computed tomographic scanning techniques.

## Case report

A 56 year old woman presented to hospital in 1977 complaining of dyspnoea of seven days' duration. She had previously been well and in particular there was no history of rheumatic fever, ischaemic heart disease, or pulmonary disease. There was no antecedent chest pain. On examination she was found to be in left heart failure with rapid atrial fibrillation. An apical systolic murmur was heard. She responded to treatment with digoxin and a diuretic. During convalescence an M mode echocardiogram showed evidence of mild mitral stenosis. Direct current conversion was performed and she was discharged with a diagnosis of mild mitral valve disease and decompensation precipitated by the onset of atrial fibrillation. She was kept under regular review and in 1978 she was found to be in atrial fibrillation again.

In 1979 a second echocardiogram was performed and again showed evidence of mild mitral stenosis. In September 1983 the patient complained of increasing dyspnoea and vague upper chest discomfort. A chest radiograph showed elevation of the right hemidiaphragm, with possible overlying pulmonary collapse and consolidation, and a right pleural effusion. There was also increased opacity in the lower part of the right hilum. She was admitted to hospital for investigation.

She was noted to be anaemic (haemoglobin 9·6 g/dl). The cardiac rhythm was atrial fibrillation, and blood pressure was 130/80 mm Hg. The venous pressure was not raised. The only remarkable findings on auscultation were an opening snap and an apical systolic murmur of moderate intensity. Physical signs in the chest were in keeping with the radiological findings. The liver was not enlarged. The erythrocyte sedimentation rate was consistently higher than 100 mm in one hour. Plasma protein electrophoresis and serum immunoglobulins were normal, as was plasma biochemistry. An electrocardiogram showed controlled atrial fibrillation with a QRS axis of 90°. Tomography demonstrated that the shadowing at the right hilum was the result of left atrial enlargement. At this stage an echocardiogram showed a large mass occupying the left atrium which appeared to be fixed posteriorly and was not attached to the interatrial septum (Fig. 1).

A digital computed tomographic scan of the thorax, gated to the R wave of the electrocardiogram, was performed at the level of the left atrium. The scan confirmed the presence of the filling defect, and showed a rim of contrast material separating the lesion from the interatrial septum (Fig. 2). Bilateral pleural effusions were seen on other views.

Subsequent right heart catheterisation demonstrated a pulmonary artery pressure of 74/30 mm Hg and a mean pulmonary capillary wedge pressure of 42 mm Hg on the right and 28 mm Hg on the left. Pulmonary angiography showed normal pulmonary

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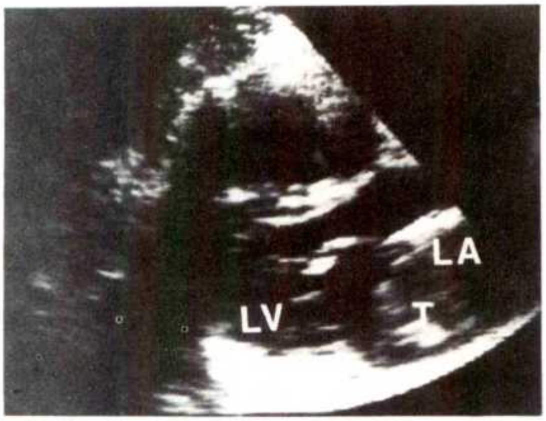

Fig. 1 *Preoperative cross sectional echocardiogram (long axis parasternal view) showing tumour (T) in the left atrium (LA). LV, left ventricle.*

arteries. Only the left pulmonary veins could be identified. The filling defect was seen to occupy most of the left atrial cavity. The mitral valve cusps were thickened. The appearance of the left ventricle and aorta was unremarkable.

At operation in November 1983 the right atrium and ventricle, and the left atrium were enlarged. Left atriotomy showed a friable, necrotic tumour with areas of fibrosis that almost completely filled the atrium. The tumour was removed without difficulty from the region surrounding the orifice of the left pulmonary veins but it was densely adherent to the orifice of the right inferior pulmonary vein, from which it appeared to arise. There was no septal or valvar involvement.

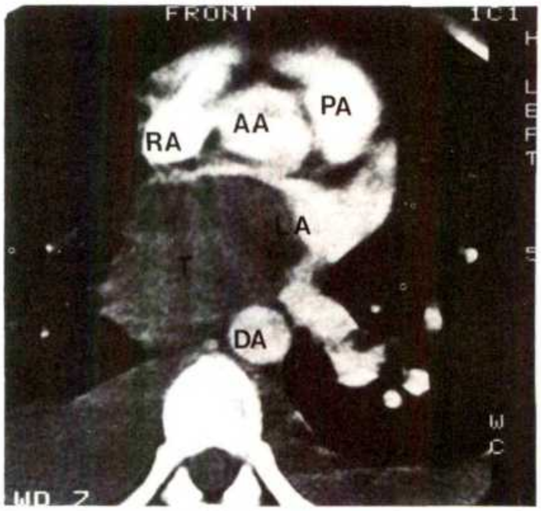

Fig. 2 *Preoperative digital gated computed tomogram of the thorax at the level of the left atrium. Tumour (T) is seen filling the left atrium (LA). The horn-shaped left atrial appendage is free of tumour. RA, right atrium; AA, ascending aorta; PA, pulmonary artery; DA, descending aorta.*

After removal of the tumour, the mitral valve was found to be stenosed, with 5 mm fusion of each commissure. Complete splitting of the commissures was obtained.

Postoperative convalescence was uneventful. Sinus rhythm was restored by direct current conversion. Histological examination of the tumour showed clusters of cells with strongly eosinophilic cytoplasm and striation. Mitotic activity was conspicuous. These appearances are typical of rhabdomyosarcoma. A postoperative echocardiogram showed no evidence of residual tumour. She was given a course of radiotherapy and remains symptom free.

## Discussion

Primary cardiac sarcomas are very rare tumours. Angiosarcomas are the most common form and rhabdomyosarcomas the second most common form.[1 2] Rhabdomyosarcomas have been reported in patients ranging in age from 3 months to 80 years but, like other primary sarcomas, they usually occur in adults.[2] A slight male preponderance has been reported.[1] In a recent review of published reports, Schwartz *et al* found that 26 out of 40 reported cases of primary cardiac rhabdomyosarcoma occurred in males.[3] Unlike angiosarcomas, rhabdomyosarcomas do not appear to have a predilection for any particular cardiac chamber, and they occur with equal frequency on the right and left sides of the heart. In approximately 60% of cases coming to necropsy the tumour affects multiple cardiac sites.[2]

Cardiac tumours often remain undetected during life and the diagnosis is made at necropsy. Echocardiography greatly increased the potential for prompt and correct diagnosis.[4] Though echocardiography demonstrated the presence of a fixed left atrial mass in this patient, we obtained much higher resolution with the computed tomographic scan. When computed tomographic scans of pulsating organs such as the heart or aorta are taken conventionally the images are blurred and indistinct. Multiple tomographic scans all taken at one particular phase of the electrocardiogram cycle, and selected by computer can be reconstructed into a full computed tomographic image of the transverse section of the thorax at that phase of the electrocardiogram cycle. The resulting scans are much more distinct and details of intracavitary and intramural abnormalities of the heart can be seen. In our patient the computed tomographic scan was gated to the R wave. The gated scan distinctly showed the tumour and the rim of contrast separating it from the interatrial septum. Since this non-invasive technique is safer than cardiac catheterisation, in which there is a risk of embolism by tumour fragments, we recommend its use when the echocardiogram is suggestive of tumour and more precise definition is required.

The need to maintain a high level of suspicion for unusual abnormalities is well illustrated by this case in which symptomatic deterioration was at first considered to have resulted from mitral valve disease.

The demonstration of a right ventricular rhabdomyosarcoma by means of computed tomographic scanning has previously been reported.[5] We believe, however, that this is the first report of a left atrial sarcoma defined by this method.

We thank Mr L Hamilton and Dr E McIlrath for their help and advice.

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*Br Heart J* 1986; 55: 308–10

# QT prolongation after ampicillin anaphylaxis

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SUMMARY Tall T waves and pronounced prolongation of the QT interval developed 24 hours after an apparently complete recovery from an acute anaphylactic reaction to oral ampicillin in a previously healthy woman of 29. These electrocardiographic abnormalities gradually subsided over five days. The prolongation of the QT interval has not previously been reported after anaphylaxis.

Acute anaphylactic reactions are sudden, frightening, and potentially lethal responses to various allergens. Very often they are provoked by drugs, most commonly penicillin or agents used for radiological investigations. Electrocardiographic changes occurring in association with anaphylaxis have been reported by several observers. These took the form of ST segment depression or elevation, T wave changes, arrhythmias, or conduction disturbances. The fact that such changes occur is not generally appreciated, and there are only a few published reports. We describe a case of severe anaphylaxis after oral ampicillin in which there were tall T waves and pronounced prolongation of QT interval—electrocardiographic findings that have not previously been reported in association with anaphylaxis.

## Case report

A 29 year old previously healthy senior house officer collapsed 30 minutes after taking a first dose of 250 mg of oral ampicillin for an upper respiratory tract infection. She was pale and clammy with an unrecordable blood pressure and had a bowel evacuation during the episode. She quickly recovered after immediate resuscitative measures, including intravenous hydrocortisone 200 mg and adrenaline 1 ml 1:1000, and oxygen inhalation. Fifteen minutes later she again became hypotensive (systolic blood pressure 40 mm Hg) and drowsy but she responded to hydrocortisone and adrenaline. Physical examination was unremarkable and two 12 lead electrocardiograms taken that day were normal.

Twenty four hours later, however, when she had apparently completely recovered, her electrocardiogram showed generalised tall peaked T waves and pronounced prolongation of the QT interval by 41% ($QT_c$ 0·58 s, upper limit of normal for age and sex 0·41 s (Figure)). Serum sodium, potassium, and calcium and renal function tests were all normal. There was no evidence of myocardial necrosis from cardiac enzyme estimations, and an echocardiogram and a ventilation perfusion lung scan were also normal. Paired serum samples were taken immediately after the episode and two weeks later and showed no evidence of recent viral infection. The electrocardiographic changes lasted five days and gradually subsided. She was treated with prednisolone 30 mg per day and discharged on the eighth day with no clinical or electrocardiographic abnormalities. Further inquiries showed that she had collapsed one year before after taking a single dose of ampicillin for urinary symptoms. She had recovered spontaneously and no specific diagnosis had been made at that time.

## Discussion

Anaphylactic reactions may occur after parenteral administration of drugs and they have also been reported after oral intake.[1] There are two main clinical presentations of anaphylaxis: *(a)* respiratory with bronchospasm or laryngeal oedema or both; and *(b)* cardiovascular with collapse and shock. Diffuse urticaria may be associated with both, and both presentations can be rapidly fatal.

The incidence of electrocardiographic changes after anaphylaxis is not known exactly, but such changes seem to be more common in patients presenting with cardiovascular collapse.[2] Bernreiter first reported an elderly patient who developed tran-

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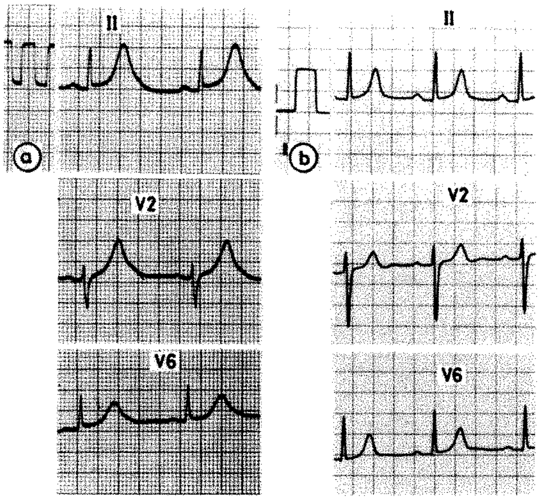

Figure *Electrocardiograms (a) 24 h after anaphylaxis ($QT_c$ = 0·58 s) and (b) 10 days after anaphylaxis ($QT_c$ = 0·41 s).*

sient atrial fibrillation, intraventricular conduction disturbances, and T wave changes after acute anaphylaxis.[3] Fourteen cases of anaphylaxis were reviewed by Booth and Patterson, and electrocardiographic changes were seen in six.[4] These were variable and included ST segment elevation and depression, nodal rhythm, and atrial fibrillation. The prolonged QT interval seen in our patient who survived severe anaphylaxis has not been described before.

The pathological basis of these electrocardiographic changes is uncertain. Electrocardiographic changes developed in eight out of nine monkeys in which anaphylaxis had been experimentally induced.[5] Again there was no characteristic pattern. Distinct myocardial necrosis was seen in these animals at necropsy. No evidence of such lesions was found by Delage and Irey in a review of necropsies of patients who died of anaphylaxis.[6] Booth and Patterson postulate the following mechanisms as being responsible for the electrocardiographic changes—a direct antigen-antibody myocardial reaction, effect of anaphylactic mediators or sympathomimetics administered as treatment, anoxia, pre-existing heart disease, or a combination of these factors.[4]

There was no other obvious cause other than anaphylaxis to account for the electrocardiographic changes in our patient. Prolonged QT intervals have been associated with myocardial ischaemia, electrolyte disturbances, drugs, and at times have been congenital or idiopathic. Serial measurements of cardiac enzymes in plasma samples did not suggest any myocardial necrosis in the present case and there were no biochemical disturbances, such as hypocalcaemia, that are known to prolong the QT.[7] Neither ampicillin nor hydrocortisone are known to affect electrocardiograms. Adrenaline altered QT intervals in experiments in dogs. Abildskov reported that rapid intravenous injection of adrenaline led to transient QT prolongation (for 12 seconds) followed by reduction in QT interval (2 minutes).[8] The persistent change was a shortened QT interval which was also seen with slow infusion of adrenaline. Thus it is unlikely that the prolonged QT interval seen in our patient was caused by the adrenaline used for resuscitation.

The aetiological factors responsible for these changes are debatable. QRS prolongation and other changes have been described in animals in experimental anaphylactic shock.[9] The QRS prolongation was partly attributed to vagal action, because it was less intense after vagotomy, although QRS was prolonged to some extent in heart and lung preparations. We saw no change in QRS in our patient. Histamine released during allergic reactions can produce electrocardiographic changes in human subjects. Intravenous injection of 4–22 µg/min of histamine caused tachycardia, depression or inversion of T waves, and an increase in QT duration in some experimental subjects.[10] These changes were thought to be due to the sympathetic response to histamine-induced hypotension because they could be prevented by previous administration of phenylephrine hydrochloride. The influence of sympathetic activity on the QT interval has been demonstrated by studies of stellate ganglion stimulation. Yanowitz *et al* showed that left stellate stimulation in open chest dogs increased T wave amplitude and prolonged QT inverval.[11] In the same study it was shown that right stellectomy produced similar electrocardiographic changes and the authors suggested that these neurogenic electrocardiographic abnormalities were the result of an imbalance between right and left sympathetic tone. Neurogenic factors may be responsible for the QT prolongation and T wave changes seen with cerebrovascular accidents.[12] The period of syncope in our patient, however, was not immediately accompanied by electrocardiographic changes, which came later. Thus the electrocardiographic changes demonstrated in this patient may have been secondary to histamine release during the anaphylaxis or due to a pronounced increase in sympathetic activity as a result of hypotension.

A prolonged QT interval suggests an alteration in myocardial repolarisation and has been associated with serious rhythm disturbances and sudden death in various conditions. No arrhythmias were recorded in our patient who was closely monitored, but it is possible that a proportion of sudden deaths in anaphylaxis without respiratory manifestations could be due to serious rhythm disturbances related to QT prolongation. Routine electrocardiographic monitoring of the patients surviving immediate anaphylaxis would help in identifying electrocardiographic and rhythm disturbances.

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# *Notice*

## British Cardiac Society

The Annual General Meeting for 1986 will take place in York on 2 and 3 April 1986, and the closing date for receipt of abstracts was 2 January 1986.

The Autumn Meeting will be held at the Wembley Conference Centre, London, on 25 to 27 November 1986, and the closing date for receipt of abstracts will be 1 August 1986.

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# *Correction*

Asynchronous left ventricular wall motion early after coronary thrombosis *D Gibson, H Mehmel, F Schwarz, K Li, W Kübler* — We apologise to Dr Helmuth Mehmel for the misspelling of his name in our January issue (page 4).

*Br Heart J* 1986; 55: 311–20

# Staffing and facilities in cardiology in the United Kingdom 1984

## *Third biennial survey*

DOUGLAS CHAMBERLAIN, LINDA BAILEY, DESMOND JULIAN

*From the Centre for Medical Research, University of Sussex, in collaboration with the Cardiology Committee, Royal College of Physicians of London and the British Cardiac Society*

The cardiology committee of the Royal College of Physicians of London and the council of the British Cardiac Society have previously published surveys of staffing[1 2] and facilities[2] in cardiology in England and Wales relating to 1979 and 1982. In this report we present comparable data collected from health districts in England and Wales with an index date of 1 July 1984. We also have information provided by colleagues in Scotland and Northern Ireland. The purpose of the surveys is to obtain accurate information for the specialty on the number of consultant posts and the prospects for senior registrars, and also to monitor the deficiencies in the provision of services within many health districts.

## Methods of inquiry

As in previous surveys, a cardiologist in each health region of England and Wales was sent a list of districts in his locality and asked to suggest either one or two physicians in each who might be willing to act as respondents by completing a questionnaire. Contacts were also made with physicians in the health boards of Scotland, the health and social service area boards of Northern Ireland, and the independent special health authorities in London (National Heart and Chest Hospitals and Great Ormond Street Hospital).

The questionnaire comprised 20 sections relating to consultant staff, senior registrars, technical staff, referral patterns, facilities, and equipment. We distinguished between cardiovascular physicians who spend virtually all of their professional time engaged in cardiology and those who have additional responsibilities in general medicine. Three criteria were required for inclusion in the latter group: a special interest in cardiology, appropriate training in the specialty, and at least 40% of professional time devoted to it. We recognise that many other physicians, unable to meet all three criteria, provide important services to those with heart disease; however, they have not been included in the study.

Some questionnaires were returned promptly, but where necessary second and third documents were sent with reminders. Telephone contact was made with the few health districts from which no written information could be obtained. After the data had been entered on to the computer a printout of the information received from each health district was returned to the respondent for checking. Subsequently the results were assembled by region or other appropriate groups and submitted under confidential cover to our regional advisors for scrutiny as a guard against inadvertent errors. On this occasion there were few disagreements on fact, and all were readily resolved by further consultation. Finally, discrepancies with previous inquiries at district level were identified and referred for final checks.

The data for England and Wales have been refined by sequential investigation over seven years (1977 to 1985) and must be substantially accurate. We are less confident about some details from Scotland and Northern Ireland: full information has been sought on only one occasion and therefore we have had less opportunity for identifying inconsistencies. We do not underestimate our respondents difficulties in completing complex forms under pressure from many competing priorities. That our survey is complete is a testimony to the high level of cooperation we have received throughout the entire period of the survey.

Compared with our previous publication,[2] a few differences in format have been adopted for the tables, which contain the principal results of the inquiry. The most important modification concerns the designation of cardiologists as engaging in adult

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Table 1 *Number of cardiovascular physicians in post (at 1 July 1984) for each health region in England and Wales. (Data in parentheses refer to 1982 figures)*

| *Region and population* | *No of health districts* | *Major centres* | *Physicians Full time cardiology* | | *Physicians Major interest* | | *No of physicians engaged in cardiology* |
|---|---|---|---|---|---|---|---|
| | | | *Adult* | *Paediatric* | *Adult* | *Paediatric* | |
| East Anglia (1 939 600) | 8 | 1 | 3 | 0 | 3 | 0 | 6 |
| Mersey (2 428 100) | 10 | 1 | 4 | 2 | 2 | 1 | 9 |
| Northern (3 093 100) | 16 | 1 | 6 | 2 | 11 | 0 | 19 |
| North East Thames (3 738 400) | 16 | 3 | 12 | 0 | 10 | 1 | 23 |
| North West Thames (3 471 000) | 15 | 4 | 11 | 2 | 9 | 1 | 23 |
| North Western (3 996 700) | 19 | 3 | 9 | 1 | 11 | 1 | 22 |
| Oxford (2 405 400) | 8 | 1 | 3 | 1 | 6 | 1 | 11 |
| South East Thames (3 595 300) | 15 | 4 | 13 | 3 | 10 | 0 | 26 |
| South West Thames (2 953 800) | 13 | 1 | 5 | 0 | 4 | 0 | 9 |
| South Western (3 125 100) | 11 | 1 | 2 | 2 | 9 | 0 | 13 |
| Trent (4 610 600) | 12 | 2 | 5 | 1 | 13 | 1 | 20 |
| Wessex (2 824 400) | 10 | 1 | 2 | 2 | 7 | 0 | 11 |
| West Midlands (5 176 000) | 22 | 3 | 11 | 2 | 9 | 0 | 22 |
| Yorkshire (3 598 900) | 17 | 3 | 7 | 3 | 9 | 0 | 19 |
| Wales (2 807 200) | 9* | 1 | 4 | 0 | 8 | 0 | 12 |
| National Heart and Chest Hospitals and Great Ormond Street Hospital | 5† | 4 | 14‡ | 8 | 0 | 0 | 22 |
| Totals | 206 (206) | 34 (34) | 111 (111) | 29 (18) | 121 (117) | 6 (4) | 267 (250) |

*Wales has nine health districts and 18 district general hospitals.

†The National Heart and Chest Hospitals and Great Ormond Street Hospital do not comprise a region with districts. They are administered separately as independent special health authorities.

‡Two additional posts were created but two others have been re-designated as paediatric cardiology.

or paediatric practice. Previously we had a column for those claiming both skills. This has been abandoned partly in recognition of the tighter delineation of paediatric cardiology as a subspecialty, but also because of the apparently random movement of individuals into and out of the "both" column that represents a category lacking an adequate definition. We accept that most cardiologists in adult practice see some children with congenital heart disease, and that this requires no special statement. To permit comparisons between the 1982 and 1984 data the earlier figures adjusted to the 1984 format are shown in parentheses wherever it seems relevant to do so. The inquiry on facilities has been broadened to include percutaneous transluminal angioplasty, the one major advance in cardiology that has been developed between the two surveys.

Detailed information compiled under individual health districts has not been published but can be made available to those with a legitimate interest in the provision of cardiological services. Some information, notably names of individual consultants and senior registrars, with associated retirement or contract expiry date, is regarded as confidential and will not be divulged except as composite data in tables.

## Comment

Table 2 *Number of cardiovascular physicians in health boards of Scotland at 1 July 1984. (Data in parentheses refer to 1982 figures)*

| *Health boards and population* | *Major centres* | *Physicians Full time cardiology* | | *Physicians Major interest* | | *No of physicians engaged in cardiology* |
|---|---|---|---|---|---|---|
| | | *Adult* | *Paediatric* | *Adult* | *Paediatric* | |
| Grampian (497 272) | 1 | 1 | 0 | 2 | 0 | 3 |
| Highland (197 208) | 0 | 0 | 0 | 1 | 0 | 1 |
| Orkney (19 134) | 0 | 0 | 0 | 0 | 0 | 0 |
| Shetland (23 351) | 0 | 0 | 0 | 0 | 0 | 0 |
| Tayside (394 415) | 0 | 1 | 0 | 2 | 0 | 3 |
| Greater Glasgow (979 059) | 2 | 7 | 2 | 9 | 1 | 19 |
| Ayrshire and Arran (375 776) | 0 | 0 | 0 | 3 | 0 | 3 |
| Argyll and Clyde (447 951) | 0 | 0 | 0 | 0 | 0 | 0 |
| Lothian (744 558) | 1 | 6 | 2 | 2 | 0 | 10 |
| Borders (101 278) | 0 | 0 | 0 | 0 | 0 | 0 |
| Fife (344 488) | 0 | 0 | 0 | 1 | 0 | 1 |
| Forth Valley (272 792) | 0 | 0 | 0 | 0 | 0 | 0 |
| Lanark (570 636) | 0 | — | — | 2 | — | 2 |
| Western Isles (314 456) | 0 | 0 | 0 | 0 | 0 | 0 |
| Total | 4 | 15 (15) | 4 (1) | 22 (22) | 1 (2) | 42 (40) |

The second survey introduced data on technical staffing and facilities for England and Wales, infor-

Table 3 *Number of cardiovascular physicians in post in Northern Ireland at 1 July 1984. (Data in parentheses refer to 1982 figures)*

| *Health and social service boards and population* | *No of units of management* | *Major centres* | *Physicians Full time cardiology* | | *Physicians Major interest* | | *No of physicians engaged in cardiology* |
|---|---|---|---|---|---|---|---|
| | | | *Adult* | *Paediatric* | *Adult* | *Paediatric* | |
| Northern (381 100) | 4 | — | 0 | 0 | 3 | 0 | 3 |
| Southern (286 600) | 3 | — | 2 | 0 | 2 | 0 | 4 |
| Western (261 200) | 3 | — | 0 | 0 | 2 | 0 | 2 |
| Eastern (649 600) | 14 | 1 | 11 | 1 | 0 | 0 | 12 |
| Total | 24 | 1 | 13 (11) | 1 (1) | 7 (6) | 0 (0) | 21 (18) |

mation that was not obtained from our first questionnaire. This third survey is even broader: we have attempted to collect comprehensive information for the whole of the United Kingdom. The increasing complexity of the inquiry has been associated with problems in data collection and analysis that make early publication difficult to achieve. We hope, however, that any future biennial or triennial surveys will be completed more readily by following a pattern that is now reasonably well established.

Tables 1, 2, and 3 show the number of cardiovascular physicians in each region of England and Wales, in each health board in Scotland, and in each health and social service area board in Northern Ireland. As explained in the Methods, these tables are not directly comparable with those published previously because the column for cardiologists claiming skills in both adult and paediatric practice has been eliminated; all individuals have been classified into one of the two principal divisions of the speciality. Comparisons can be made, however, in the line showing totals for each of the remaining categories: numbers from the 1982 survey (adjusted to the 1984 format) are shown in parentheses. For England and Wales (Table 1) a modest improvement has been made in the number of cardiologists in adult practice. Two new posts in full time cardiology are not reflected in the table because two others have been re-designated as paediatric cardiology. There is a net increase of four posts for those with a major interest (representing six gains and two losses). The major expansion, however, has come in nine new posts in paediatric cardiology; there are also two apparent additions that result only from errors of designation in our last survey. We have attempted similar comparisons for Scotland (Table 2) and for Northern Ireland (Table 3) and we believe them to be substantially accurate. Five new posts appear in these tables (a net gain of two in paediatric cardiology). Thus for the whole United Kingdom we have the following net increases in posts: full time adult cardiology, four; full time paediatric cardiology, 12; major interest adult cardiology, five; major interest paediatric cardiology, one; overall total, 22.

The numbers of physicians engaged full time in cardiology in England and Wales in this survey is now 140 (adult plus paediatric). The figure published for 1984 by the Department of Health and Social Security is close to this at 135.[3] The reason for the small discrepancy does not lie with our earlier index date (July compared with September 1984), but probably with differences in designation

Table 4 *Number of retirements expected each year for cardiovascular physicians in post in England and Wales at 1 July 1984*

| *Year* | *Full time cardiology* | | | *Major interest cardiology* | | | *Grand total* |
|---|---|---|---|---|---|---|---|
| | *A* | *P* | *Total* | *A* | *P* | *Total* | |
| 1984 | 3 | 0 | 3 | 0 | 0 | 0 | 3 |
| 1985 | 3 | 1 | 4 | 2 | 1 | 3 | 7 |
| 1986 | 6 | 1 | 7 | 3 | 1 | 4 | 11 |
| 1987 | 2 | 0 | 2 | 3 | 0 | 3 | 5 |
| 1988 | 5 | 0 | 5 | 4 | 0 | 4 | 9 |
| 1989 | 4 | 1 | 5 | 1 | 0 | 1 | 6 |
| 1990 | 3 | 0 | 3 | 2 | 0 | 2 | 5 |
| 1991 | 5 | 0 | 5 | 2 | 0 | 2 | 7 |
| 1992 | 1 | 0 | 1 | 5 | 0 | 5 | 6 |
| 1993 | 2 | 0 | 2 | 1 | 0 | 1 | 3 |
| 1994 | 1 | 0 | 1 | 3 | 0 | 3 | 4 |
| 1995 | 4 | 1 | 5 | 1 | 1 | 2 | 7 |
| 1996 | 3 | 1 | 4 | 2 | 0 | 2 | 6 |
| 1997 | 3 | 0 | 3 | 1 | 0 | 1 | 4 |
| 1998 | 6 | 1 | 7 | 4 | 0 | 4 | 11 |
| 1999 | 2 | 1 | 3 | 11 | 0 | 11 | 14 |
| 2000+ | 58 | 22 | 80 | 76 | 3 | 79 | 159 |
| Total | 111 | 29 | 140 | 121 | 6 | 127 | 267 |

A, adult; P, paediatric.

Table 5 *Number of retirements expected each year for cardiovascular physicians in post at 1 July 1984 in Scotland*

| *Year* | *Full time cardiology* | | | *Major interest cardiology* | | | *Grand total* |
|---|---|---|---|---|---|---|---|
| | *A* | *P* | *Total* | *A* | *P* | *Total* | |
| 1984 | 0 | 0 | 0 | 1 | 0 | 1 | 1 |
| 1985 | 3 | 0 | 3 | 1 | 0 | 1 | 4 |
| 1986 | 0 | 0 | 0 | 1 | 0 | 1 | 1 |
| 1987 | 0 | 0 | 0 | 1 | 0 | 1 | 1 |
| 1989 | 1 | 0 | 1 | 0 | 0 | 0 | 1 |
| 1990 | 2 | 0 | 2 | 1 | 1 | 2 | 4 |
| 1993 | 0 | 0 | 0 | 1 | 0 | 1 | 1 |
| 1994 | 0 | 0 | 0 | 1 | 0 | 1 | 1 |
| 1995 | 1 | 0 | 1 | 0 | 0 | 0 | 1 |
| 1998 | 1 | 0 | 1 | 1 | 0 | 1 | 2 |
| 1999 | 0 | 1 | 1 | 0 | 0 | 0 | 1 |
| 2000+ | 7 | 3 | 10 | 14 | 0 | 14 | 24 |
| Total | 15 | 4 | 19 | 22 | 1 | 23 | 42 |

A, adult; P, paediatric.

Table 6 *Number of retirements expected each year for cardiovascular physicians in post in Northern Ireland at 1 July 1984*

| *Year* | *Full time cardiology* | | | *Major interest cardiology* | | | *Grand total* |
|---|---|---|---|---|---|---|---|
| | *A* | *P* | *Total* | *A* | *P* | *Total* | |
| 1986 | 0 | 0 | 0 | 1 | 0 | 1 | 1 |
| 1992 | 1 | 0 | 1 | 0 | 0 | 0 | 1 |
| 1997 | 1 | 0 | 1 | 0 | 0 | 0 | 1 |
| 1998 | 2 | 0 | 2 | 0 | 0 | 0 | 2 |
| 2000+ | 9 | 1 | 10 | 6 | 0 | 6 | 16 |
| Total | 13 | 1 | 14 | 7 | 0 | 7 | 21 |

A, adult; P, paediatric.

of physicians as full time in cardiology or with a major interest in the specialty. Designation may become increasingly arbitary and consistency more difficult to attain with the new emphasis on a spectrum of activity rather than polarisation between the old type A and type B categorisation. Inclusion of the whole spectrum of cardiologists who have special training and expertise does seem the more realistic approach. The numbers have now reached 267 in this survey.

Tables 4, 5, and 6 show the expected retirement dates of consultant cardiologists for respectively, England and Wales, Scotland, and Northern Ireland. We have data both by assuming retirement at age 65 and by taking account of stated intentions to retire early. Neither method will accurately foretell future events, but as in the last survey we have published intended dates as being the better approximation. Though some intentions have been modified, the pattern for England and Wales is broadly similar to that in our previous publication. Both show 38 impending retirements for the five years 1985–89, with only two minor adjustments which do not affect overall figures. Opportunities for senior registrars from retirements alone do not increase until 1998 when the pattern changes markedly: a large turnover of posts continues from then until 2013 at least, well beyond the scope of the published tables (full details can be supplied on request). From 1998 most of the vacancies will be in posts designated as having a major interest in cardiology, whereas posts requiring exclusive time in cardiology are slightly more numerous until that date. The numbers for Scotland and Northern Ireland are too small for trends to be identified.

Table 7 shows the number of health districts without cardiologists as defined for this survey. Wales cannot be considered in the same way as England because it has twice as many major district hospitals as health districts. For better comparability, hospitals rather than districts have been counted for the Principality as in our previous publication. Eight districts in England or district hospitals in Wales that were without cardiologists in 1982 had one in post by 1984, but two others lost them. The net gain was therefore six within the 63 previously without cardiologists. If Wales is excluded because the health authorities are not strictly comparable with those of England, there was a gain of five new posts within the 52 health districts previously without local cardiological expertise. The populations within the health districts still without cardiologists total 9·3 million excluding Wales, and 10·7 with it. This represents only a small improvement in the overall 1982 figure of 11·7 million. In addition nine other health districts have five or less cardiology sessions per week. Within the totals it can be seen that the North East Thames

Table 7 *Number of health districts and population without cardiovascular physicians working full time in specialty or with a major interest as defined for the survey at 1 July 1984. (Data in parentheses refer to 1982 in figures)*

| *Region and population* | *No of health districts in region* | *No of health districts without cardiovascular physicians* | *Total health district population not served by cardiovascular physicians* |
|---|---|---|---|
| East Anglia (1 939 600) | 8 | 4 (+1) | 905 900 |
| Mersey (2 428 100) | 10 | 7 | 1 510 000 |
| Northern (3 093 100) | 16 | 5 (−2) | 860 800 |
| North East Thames (3 738 400) | 16 | — | — |
| North West Thames (3 471 000) | 15 | 3 | 701 700 |
| North Western (3 996 700) | 19 | 5 (+1) | 861 300 |
| Oxford (2 405 400) | 8 | 2 | 522 300 |
| South East Thames (3 595 300) | 15 | 1 (−2) | 218 400 |
| South West Thames (2 953 800) | 13 | 4 (−1) | 855 900 |
| South Western (3 125 100) | 11 | 1 | 206 400 |
| Trent (4 610 600) | 12 | 3 | 748 300 |
| Wessex (2 824 400) | 10 | 3 | 651 000 |
| West Midlands (5 176 000) | 22 | 4 (−2) | 655 800 |
| Yorkshire (3 598 900) | 17 | 5 | 808 000 |
| Wales (2 807 200) | 9/18* | 10 (−1) | 1 152 200 |
| National Heart and Chest Hospitals and Great Ormond Street Hospital | 5† | — | 10 658 000 |
| Totals | 206 (215) | 57 (63) | 9 264 500 |

*Wales has nine health districts and 18 district general hospitals. The populations served by these hospitals are estimates.

†The National Heart and Chest Hospitals and Great Ormond Street Hospital do not comprise a region with districts. They are administered separately as independent special health authorities.

Table 8 *Health boards and population in Scotland, without cardiovascular physicians working full time in specialty or with a major interest as defined for the survey, at 1 July 1984*

| *Health boards without cardiovascular physicians* | | *Health board population not served by cardiovascular physicians* |
|---|---|---|
| Argyll and Clyde | | 447 951 |
| Borders | | 101 278 |
| Forth Valley | | 272 792 |
| Orkney | | 19 134 |
| Shetland | | 23 351 |
| Western Isles | | 314 456 |
| Total | 6 (6) | 1 178 962 |

Region is alone in having a cardiologist within each district hospital, with South East Thames and South Western near to this ideal. Mersey and Wales can be cited as particularly poorly endowed, accounting between them for nearly a third of the population not served by cardiologists. Data comparable to that in Tables 8 and 9 were not available for our last survey. These show that nine administrative areas within Scotland and Northern Ireland are without cardiologists. The population in these areas added to that in England and Wales makes a total of 12·3 million for the United Kingdom, though a recent joint report from the Royal College of Physicians of London and the Royal College of Surgeons of England recommends that every district general hospital should have at least one physician with special training in cardiology.[4]

Other special committees have addressed the needs within their own fields. For example, committees of the College of Physicians of London on gastroenterology[5] and on thoracic medicine[6] have both recommended that at least one physician within each district hospital should be trained in their respective disciplines. Both have suggested one specialist per 150 000 population so that larger district hospitals should have two. Cardiologists (with their colleagues in general medicine) face the heaviest burden of community mortality and morbidity within their sphere of expertise and have much of proven value in treatment to offer. It is also our contention that the larger district hospitals should even-

Table 9 *Health and social service boards without cardiovascular physicians working full time in specialty or with a major interest as defined for the survey in Northern Ireland at 1 July 1984*

| *Health and social service board* | *No of units of management* | *No of units without cardiovascular physicians* | *Total unit of management population not served by cardiovascular physicians* |
|---|---|---|---|
| Northern (381 100) | 4 | 1 | 63 700 |
| Southern (286 600) | 3 | 0 | — |
| Western (261 200) | 3 | 1 | 162 800 |
| Eastern (649 600) | 14 | 4 | 143 600* |
| Totals | 24 | 6 | 370 100* |

Some units of management without cardiovascular physicians do have visits from nearby cardiac centres.

*Population figures are not available from Northern Ireland for two units of management and so not included in these figures.

Table 10 *Senior registrars: contract expiry dates, type of appointment, and career intentions in England and Wales at 1 July 1984*

| *Year* | *Number* | *Type of appointment* | | | *Career intentions* | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | *NHS* | *Academic* | *Other* | *WT* | *MI* | *GM* | *CA* | *UD* |
| 1984 | 4 | 3 | 1 | 0 | 3 | 1 | 0 | 0 | 0 |
| 1985 | 17 | 8 | 4 | 3 | 10 | 3 | 0 | 3 | 1 |
| 1986 | 6 | 6 | 0 | 0 | 5 | 1 | 0 | 0 | 0 |
| 1987 | 7 | 4 | 3 | 0 | 7 | 0 | 0 | 0 | 0 |
| 1988 | 9 | 8 | 1 | 0 | 6 | 2 | 0 | 1 | 0 |
| No expiry dates | 13 | 5 | 7 | 1 | 11 | 2 | 0 | 0 | 0 |
| Total | 56* | 34 | 16 | 4 | 42 | 9 | 0 | 4 | 1 |

WT, whole time cardiology; MI, major interest cardiology; GM, general medicine (no special interest in cardiology), CA, career abroad; UD, undecided

*There is no information available about the type of appointment held by two of 56 senior registrars or equivalents.

Ten of the 56 senior registrars have already had their contracts renewed; one of these is now listed as having no contract expiry date although on a National Health Service contract, a further two, also on National Health Service contracts, are listed as having expired contracts.

Table 11 *Senior registrars: contract expiry dates, type of appointment, and career intentions in Scotland at 1 July 1984*

| *Year* | *Number* | *Type of appointment* | | | *Career intentions* | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | *NHS* | *Academic* | *Other* | *WT* | *MI* | *GM* | *CA* | *UD* |
| 1984 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| 1986 | 4 | 1 | 3 | 0 | 2 | 2 | 0 | 0 | 0 |
| 1987 | 2 | 1 | 1 | 0 | 2 | 0 | 0 | 0 | 0 |
| 1988 | 2 | 2 | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| Total | 9 | 5 | 4 | 0 | 5 | 3 | 0 | 0 | 1 |

WT, whole time cardiology; MI, major interest cardiology; GM, general medicine (no special interest in cardiology); CA, career abroad; UD, undecided.

Table 12 *Senior registrars: contract expiry dates, type of appointment, and career intentions in Northern Ireland at 1 July 1984*

| *Year* | *Number* | *Type of appointment* | | | *Career intentions* | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | *NHS* | *Academic* | *Other* | *WT* | *MI* | *GM* | *CA* | *UD* |
| 1984 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| 1985 | 6 | 5* | 0 | 0 | 2 | 2 | 1 | 1 | 0 |
| 1986 | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| 1987 | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Total | 9 | 8* | 0 | 0 | 2 | 2 | 3 | 1 | 1 |

WT, whole time cardiology; MI, major interest cardiology, GM, general medicine (no special interest in cardiology); CA, career abroad, UD, undecided

*No information available about type of appointment held by one of the senior registrars.

tually have two consultants trained in the specialty if a reasonably comprehensive service is to be offered to the community. While the consultant staffing levels within most district hospitals cannot at present support the recommendations of all specialist committees, implementation or part implementation of the Short report[7] would make these aims feasible.

Tables 10, 11, and 12 show the details of senior registrars in post in the United Kingdom. In England and Wales the number has fallen between our last three surveys from 71 to 63 to 56. Since the 1982 survey four academic posts and three other honorary contracts have also been lost or temporarily frozen. The career intention of the registrars is overwhelmingly to practice cardiology exclusively, though many must know that this is unrealistic. Both Scotland and Northern Ireland have nine senior registrars, but we have no comparable data for 1982.

Table 13 shows the distribution of consultants and senior registrars between regions. This continues to be very uneven, for example there are 10 senior registrars in North West Thames and eight in North East Thames compared with none in Wessex and one in East Anglia (East Anglia was shown as having two in the previous survey but this was an error of designation—no change has occurred). The relatively high numbers within the four Thames regions—23 or over 30% of all in the United Kingdom—reflects the preponderance of teaching hospitals and major cardiac centres in the metropolitan regions. The ratio of consultants to senior registrars should, however, be relatively constant.

Table 13 *Number of full time cardiovascular physicians and senior registrars in post in each region in England and Wales at 1 July 1984. (Data in parentheses refer to 1982 figures)*

| *Region* | *No of health districts* | *Full time physicians cardiology* | *Physicians major interest* | *Senior registrars* |
|---|---|---|---|---|
| East Anglia | 8 | 3 | 3 | 1 |
| Mersey | 10 | 6 | 3 | 3 |
| Northern | 16 | 8 | 11 | 3 |
| North East Thames | 16 | 12 | 11 | 8 |
| North West Thames | 15 | 13 | 10 | 10 |
| North Western | 19 | 10 | 12 | 2 |
| Oxford | 8 | 4 | 7 | 3 |
| South East Thames | 15 | 16 | 10 | 3 |
| South West Thames | 13 | 5 | 4 | 2 |
| South Western | 11 | 4 | 9 | 2 |
| Trent | 12 | 6 | 14 | 3 |
| Wessex | 10 | 4 | 7 | 0 |
| West Midlands | 22 | 13 | 9 | 3 |
| Yorkshire | 17 | 10 | 9 | 5 |
| Wales | 9/18* | 4 | 8 | 2 |
| National Heart and Chest Hospitals and Great Ormond Street Hospital | 5† | 22 | 0 | 6 |
| Total | 206 (215) | 140 (129) | 127 (121) | 56 (63) |

*Wales has nine health districts and 18 district general hospitals; the figure in brackets refers to district general hospitals.
†The National Heart and Chest Hospitals and Great Ormond Street Hospital do not comprise a region with districts They are administered separately as independent special health authorities.

Table 14 *Comparison between senior registrars' contract expiry dates and cardiovascular physicians' retirement dates in England and Wales at 1 July 1984*

| *Year* | *No of contracts expiring* | *No of retirements expected* | *Balance* |
|---|---|---|---|
| 1984 | 4 | 3 | (−1) |
| 1985 | 17 | 7 | (−10) |
| 1986 | 6 | 11 | (+5) |
| 1987 | 7 | 5 | (−2) |
| 1988 | 9 | 9 | (0) |
| No expiry dates | 13 | — | (−13) |
| Total | 56 | 35 | (−21) |

Table 15 *Comparison between senior registrars' contract expiry dates and cardiovascular physicians' retirement dates in Scotland at 1 July 1984*

| *Year* | *No of contracts expiring* | *No of retirements expected* | *Balance* |
|---|---|---|---|
| 1984 | 1 | 1 | — |
| 1985 | 0 | 4 | +4 |
| 1986 | 4 | 1 | −3 |
| 1987 | 2 | 1 | −1 |
| 1988 | 2 | 0 | −2 |
| Total | 9 | 7 | −2 |

Table 16 *Comparison between senior registrars' contract expiry dates and cardiovascular physicians' retiring in Northern Ireland at 1 July 1984*

| *Year* | *No of contracts expiring* | *No of retirements expected* | *Balance* |
|---|---|---|---|
| 1984 | 1 | 0 | −1 |
| 1985 | 6 | 0 | −6 |
| 1986 | 1 | 1 | — |
| 1987 | 1 | 0 | −1 |
| Total | 9 | 1 | −8 |

To allow for the differences in tenure of the two groups, one senior registrar post is needed for every seven consultant posts if a balance is to be maintained. In England, eight regions have a satisfactory ratio, as does Wales. But Mersey and North East Thames have twice this ratio (with Yorkshire and Oxford close to twice) while North West Thames has three times the desirable ratio. The figure is also too high at the postgraduate teaching hospitals, but it may be argued these have unusual facilities and responsibilities for training. The situation is very unsatisfactory in Northern Ireland which has nine

Table 17 *Technical support in health regions in England and Wales at 1 July 1984. (Data in parentheses refer to 1982 figures)*

| *Region and population* | *Physiological measurement technicians* | | | | *Cardiographers* |
|---|---|---|---|---|---|
| | *Qualified* | *Students* | *Total* | *per 100 000* | |
| East Anglia (1 939 600) | 14·5 | 5·0 | 19·5 | 1·01 | 20·9 |
| Mersey (2 428 100) | 65·2 | 18·0 | 83·2 | 3·43 | 0·2 |
| Northern (3 093 100) | 32·5 | 6·0 | 38·5 | 1·24 | 37·4 |
| North East Thames (3 738 400) | 53·1 | 14·0 | 67·1 | 1·79 | 29·7 |
| North West Thames (3 471 000) | 28·0 | 19·0 | 47·0 | 1·35 | 34·9 |
| North Western (3 996 700) | 83·0 | 14·0 | 97·0 | 2·43 | 18·6 |
| Oxford (2 405 400) | 10·9 | 2·0 | 12·9 | 0·54 | 20·4 |
| South East Thames (3 595 300) | 40·6 | 10·0 | 50·6 | 1·41 | 50·5 |
| South West Thames (2 953 800) | 21·0 | 6·0 | 27·0 | 0·91 | 17·8 |
| South Western (3 125 100) | 31·5 | 2·0 | 33·5 | 1·07 | 28·5 |
| Trent (4 610 600) | 81·6 | 22·0 | 103·6 | 2·25 | 43·5 |
| Wessex (2 824 400) | 15·8 | 5·0 | 20·8 | 0·74 | 27·7 |
| West Midlands (5 176 000) | 81·1 | 7·0 | 88·1 | 1·70 | 35·3 |
| Yorkshire (3 598 900) | 64·5 | 8·0 | 72·5 | 2·01 | 30·7 |
| Wales (2 807 200) | 65·2 | 18·5 | 83·7 | 2·97 | 34·0 |
| National Heart and Chest Hospitals and Great Ormond Street Hospital | 42·5 | 9·0 | 51·5 | 0·00 | 2·5 |
| | 731·0 (628·3) | 165·5 (179·3) | 896·5 (807·6) | | 432·6 (468·8) |

senior registrars and 21 physicians with a major commitment to cardiology (as defined in this document). The regional disparities of course mask other anomalies within individual centres.

The balance between the senior registrars contract expiry dates and cardiovascular physicians retirement dates (Tables 14, 15, and 16) is of interest though the figures must be interpreted with caution. In the five years from 1984 to 1988 a deficit of 21 posts is shown compared with a deficit of 28 over four years shown in the 1982 survey. The change is a result of a combination of circumstances: on the one hand there are fewer senior registrars and equivalents in post and on the other hand new appointments have absorbed some of the backlog. The Department of Health and Social Security, the Joint Consultants Committee, and the British Medical Association long ago recommended that consultant posts should grow at 4% per annum and junior posts at 2·5%.[8] The consultant growth in specialised cardiology from 1979 to 1984 was 5% per annum.[3] Thus the average surplus now shown, four per year for England and Wales over the whole spectrum of cardiology, might reasonably expect to be absorbed into new appointments and unexpected vacancies, and we believe these have continued to appear since the index date of the present survey. The calculation depends upon senior registrars being in post an average of four years, which is broadly the recent pattern. But the position is complicated by varying

Table 18 *Summary of facilities in regions in England and Wales at 1 July 1984. (Data in parentheses refer to 1982 figures)*

| *Region and population* | *No of health districts* | *Cardiac surgery* | *Haemodynamic investigation* | | *Percutaneous angioplasty* | *Pacing* | | *Scans* | |
|---|---|---|---|---|---|---|---|---|---|
| | | | *Major* | *Minor* | | *Permanent* | *Temporary* | *M mode* | *Cross sectional* |
| East Anglia (1 939 600) | 8 | 1 | 2 | 5 | 1 | 2 | 8 | 8 | 5 |
| Mersey (2 428 100) | 10 | 1 | 1 | 3 | 1 | 1 | 9 | 3 | 2 |
| Northern (3 093 100) | 16 | 1 | 1 | 6 | 1 | 1 | 16 | 11 | 7 |
| North East Thames (3 738 400) | 16 | 3 | 4 | 9 | 3 | 4 | 16 | 13 | 10 |
| North West Thames (3 471 000) | 15 | 4 | 5 | 9 | 3 | 6 | 15 | 8 | 8 |
| North Western (3 996 700) | 19 | 3 | 3 | 11 | 2 | 5 | 17 | 12 | 10 |
| Oxford (2 405 400) | 8 | 1 | 1 | 5 | 1 | 1 | 7 | 6 | 3 |
| South East Thames (3 595 300) | 15 | 4 | 4 | 9 | 4 | 6 | 15 | 10 | 8 |
| South West Thames (2 953 800) | 13 | 1 | 2 | 7 | 1 | 2 | 13 | 9 | 5 |
| South Western (3 125 100) | 11 | 1 | 1 | 6 | 1 | 5 | 11 | 7 | 8 |
| Trent (4 610 600) | 12 | 2 | 3 | 7 | 2 | 3 | 10 | 8 | 5 |
| Wessex (2 824 400) | 10 | 1 | 1 | 4 | 1 | 2 | 10 | 6 | 3 |
| West Midlands (5 176 000) | 22 | 3 | 8 | 15 | 1 | 9 | 21 | 16 | 9 |
| Yorkshire (3 598 900) | 17 | 3 | 3 | 8 | 2 | 5 | 14 | 9 | 8 |
| Wales (2 807 200) | 9* | 1 | 1 | 7 | 2 | 2 | 17 | 11 | 9 |
| National Heart and Chest Hospitals and Great Ormond Street Hospital | 5† | 4 | 4 | 5 | 4 | 4 | 4 | 4 | 4 |
| | 206 (215) | 34 (34) | 44 (43) | 116 (92) | 30 | 58 (54) | 203 (198) | 141 (143) | 104 (59) |

*Wales has nine health districts and 18 district general hospitals.

†The National Heart and Chest Hospitals and Great Ormond Street Hospital do not comprise a region with districts. They are administered separately as independent special health authorities.

contract expiry dates and changing designation of appointees especially for those with honorary contracts. Though 1985 seems in Table 14 to be a particularly unbalanced year (accounting for much of the difference between trained individuals competing for appointments and posts available) the position has been eased by the creation of six new posts since July 1984. Moreover, four (in England and Wales) of the senior registrars in our present survey expressed an intention of practising abroad. The outlook for senior registrars is therefore less bleak than in the recent past. The situation seems satisfactory in Scotland. It remains unfavourable in Northern Ireland and will be eased only if highly trained individuals compete for posts elsewhere in the United Kingdom on equal terms with their peers.

Technical support (Table 17) remains very uneven throughout England and Wales. Oxford and Wessex are again at the botton of the league table; Oxford has not improved its position at all (approximately one half whole time eqivalent physiological measurement technician per 100 000 population) whereas Wessex has shown some modest improvement. Modern cardiology increasingly depends upon technicians—for monitoring of pacemaker patients, for effort testing, for ambulatory monitoring, and for echocardiography as well as for invasive studies. We are disturbed to see a relatively small overall increase (less than 10%) in technical support over a two year period when demand on the service must be increasing considerably. Not all of this presumed shortfall can be accounted for by more automation, though modern technology can potentially absorb an appreciable increase in workload for some facilities. Moreover there are now fewer cardiographers, suggesting that more electrocardiograms are taken by staff designated as technicians (a familiar strategy to overcome the inequitably poor pay of cardiographers). Much of the very small true increase must also be in support of new cardiological posts, so expansion is clearly not occurring adequately in a sphere that sorely demands it if reasonable expectations of patients are to be met.

The facilities available in England and Wales appear in Table 18. Comparisons between the 1982 and 1984 surveys can be made by examining the bottom line of Table 18 (1982 figures in parentheses). The apparent loss of one centre undertaking major haemodynamic investigations reflects only a change in designation of one unit carrying out some invasive procedures that do not include coronary angiography. Thirty centres in England and Wales were undertaking percutaneous transluminal angioplasty in 1984 (no 1982 comparison). Four more centres undertook permanent pacing and another 10 temporary pacing. Though the situation has improved, we should remember that immediate access to temporary pacing is a life saving procedure. Yet temporary pacing is still not available at all within 11 health districts (comprising over two million people). Moreover, we can reasonably assume that performance is less than ideal in many of the 50 health districts in England and Wales that undertake temporary pacing yet have no cardiologist Nor should we be satisfied with constraints upon districts that do have a cardiologist but lack immediate access to image intensification. Asystolic arrest or even severe bradycardia are emergencies in which sec-

| *Scintigraphy* | *Invasive electrophysiology* | *Recording facilities only* | *Recording facilities and analysis* | *Stress test (treadmill or bicycle)* | *Cardiac care units* | *Monitored beds* | *Coronary ambulance* |
|---|---|---|---|---|---|---|---|
| 3 | 0 | 8 | 4 | 8 | 8 | 6 | 1 |
| 0 | 1 | 7 | 5 | 9 | 9 | 17 | 1 |
| 17 | 1 | 16 | 6 | 15 | 21 | 8 | 1 |
| 16 | 3 | 15 | 14 | 16 | 15 | 37 | 1 |
| 13 | 4 | 15 | 12 | 13 | 14 | 29 | 0 |
| 6 | 3 | 17 | 15 | 17 | 19 | 1 | 3 |
| 5 | 1 | 7 | 7 | 7 | 5 | 27 | 1 |
| 22 | 5 | 15 | 14 | 15 | 17 | 9 | 3 |
| 9 | 2 | 13 | 10 | 13 | 11 | 19 | 4 |
| 18 | 3 | 11 | 9 | 10 | 12 | 16 | 4 |
| 17 | 2 | 9 | 7 | 10 | 15 | 8 | 2 |
| 6 | 1 | 10 | 5 | 9 | 10 | 22 | 3 |
| 20 | 5 | 21 | 14 | 18 | 25 | 4 | 2 |
| 17 | 2 | 15 | 13 | 15 | 13 | 38 | 2 |
| 16 | 1 | 16 | 12 | 3 | 12 | 22 | 1 |
| 11 | 4 | 4 | 4 | 4 | 2 | 12 | 0 |
| 196 (54) | 38 (42) | 199 (188) | 151 (133) | 182 (185) | 208 (162) | 275 (59) | 29 (21) |

onds and minutes without definitive treatment can determine an unfavourable outcome. The number of centres with facilities for cross sectional echocardiography has nearly doubled since 1982, while cardiac scintigraphy shows an even greater increase. The number of cardiac care units (the definition includes immediate availability of image intensification[9]) has increased from 162 to 208, and the numbers of monitored beds (no image intensification available) has gone up even more steeply—though this may reflect a change in response to a question that was ambiguous in earlier questionnaires. The number of coronary ambulance systems (or resuscitation ambulance systems) has also increased from 21 to 29; a steep rise is to be expected from now onwards because of the changed attitude of Department of Health to this facility.

The United Kingdom still suffers from gross underprovision of cardiological services. We have no access to comprehensive recent European data, but a previous report drew attention to the comparison with most other countries in the European Economic Community that have two to 10 times more cardiologists in relation to their populations.[2] Our own service should be criticised principally for the inequality of provision within the United Kingdom. We have disparities between our four countries, with 13·3 cardiologists per million population in Northern Ireland, 8·0 per million in Scotland, 5·4 per million in England, and 4·2 per million in Wales (5·82 per million overall). We have even greater inequalities between regions, and especially between districts. Correction of these anomalies, by bringing districts less well endowed into line with districts that are able to provide adequate cardiological cover is a reasonable aim and readily attainable with the present numbers of trained senior registrars and a modest increase in support facilities.

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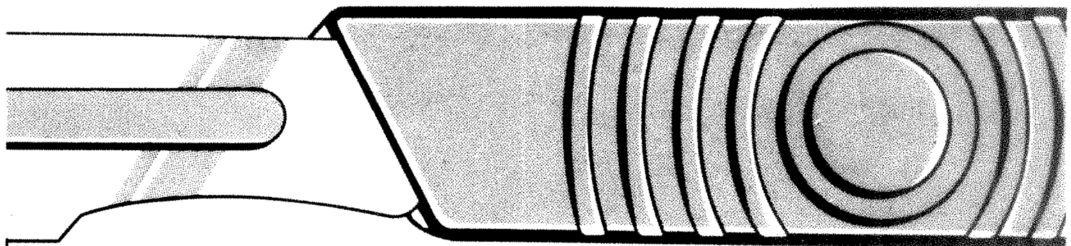

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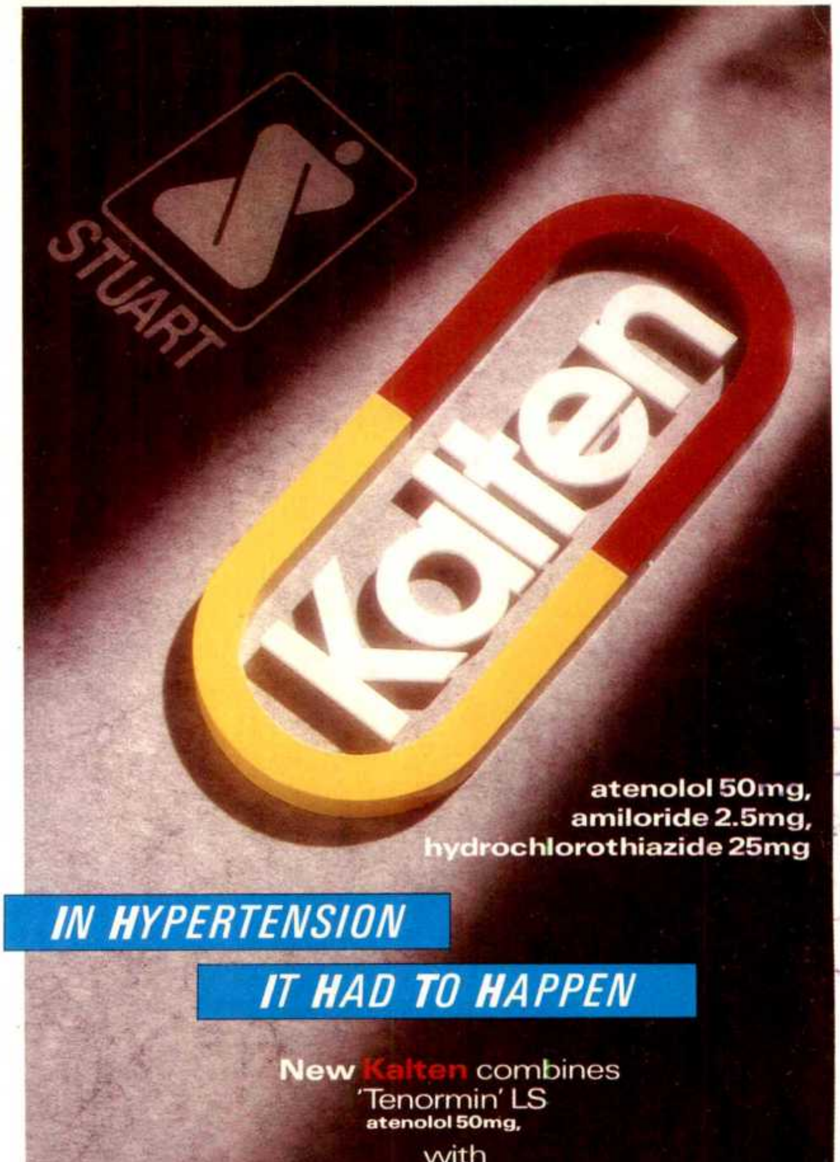

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ASTM CODEN: BHJUAV 55(4) 321—420 (1986)
ISSN 0007-0769

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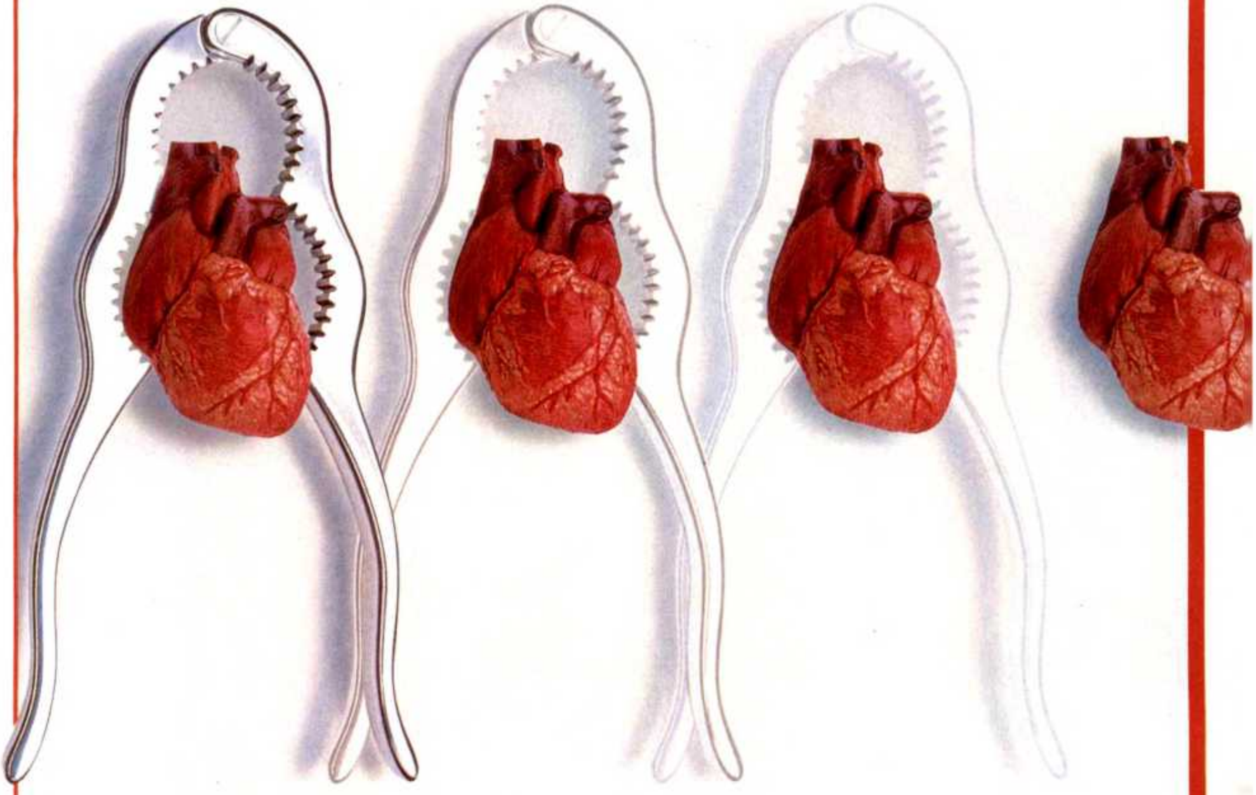

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*Br Heart J* 1986; 55: 321–9

# Dipyridamole combined with exercise for thallium-201 myocardial imaging

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SUMMARY A new stress test for thallium-201 myocardial imaging in which pharmacological coronary vasodilatation with dipyridamole is combined with dynamic exercise is described. In 38 patients with coronary artery disease the sensitivity, total number of defects, degree of redistribution, and visual quality of thallium-201 imaging were greater after dipyridamole with exercise testing than after exercise alone. When the data from these 38 patients were combined with the results of dipyridamole-exercise imaging in 49 patients in whom exercise electrocardiography had been inconclusive then the technique gave a sensitivity for coronary disease of 87% and a specificity of 92%. Dipyridamole also increased the sensitivity of the exercise electrocardiogram, so that no patient with coronary disease had a strictly negative dipyridamole-exercise stress test. Only five of 214 patients who have now undergone this test have had complications requiring reversal of vasodilatation with aminophylline. The combined use of dipyridamole and exercise in this simple technique is a reliable and safe improvement on standard thallium-201 imaging tests.

Thallium-201 myocardial imaging is now an established technique for the diagnosis of coronary artery disease.[1 2] Although thallium-201 scintigraphy performed after maximal exercise (exercise imaging) may possess greater sensitivity for coronary disease than does exercise electrocardiography,[3 4] false negative scintigrams are still found in about 25% of patients.[5–7] While computer assisted quantitation of scintigrams is said to give greater sensitivity than simple visual analysis,[8 9] falsely negative results can still be expected when the stress imposed before thallium-201 injection is insufficient to produce regional differences in thallium-201 distribution.

The two widely used stress methods for thallium-201 imaging are dynamic exercise and pharmacological coronary vasodilatation with dipyridamole.[10] The purpose of these studies was to evaluate a simple technique in which maximal exercise testing is performed in the presence of a high plasma concentration of dipyridamole (a dipyridamole-exercise stress test). Studies of three groups of patients are described: in section 1 the sensitivity and quality of thallium-201 images obtained with the new method were compared with standard exercise imaging. The overall sensitivity and specificity of dipyridamole-exercise imaging were assessed in section 2, and in section 3 the optimal time for exercise testing after the large oral dose of dipyridamole was determined by serial measurement of plasma concentrations.

## Section 1: a comparison of dipyridamole-exercise imaging with standard thallium-201 imaging in patients with coronary artery disease

### PATIENTS AND METHODS

Thirty eight patients with stable mild or moderate angina pectoris were studied (35 male and three female; aged between 38 and 62 years, mean 50·5 years). The selection criteria were as follows: (*a*) no electrocardiographic or angiographic evidence of previous myocardial infarction; (b) no myocardial ischaemia (angina or ischaemic ST segment changes) during the first six minutes of a treadmill exercise test (modified Bruce protocol); (*c*) unequivocal evidence of coronary artery disease. Important lesions had been demonstrated in all 32 patients who had undergone coronary arteriography. The remaining six patients were middle aged men with typical angina and an ischaemic ST

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Accepted for publication 7 January 1986

segment response during exercise, who may therefore be assumed to have had coronary disease[11 12] but whose symptoms did not warrant arteriography.

These criteria were designed to select those patients in whom standard thallium-201 imaging could be expected to show a relatively low sensitivity for coronary disease.[3 13] By excluding patients with easily induced myocardial ischaemia the probability of angina being produced by dipyridamole alone was also reduced (unpublished observations).

Each patient gave informed consent to undergo exercise thallium-201 imaging on two separate occasions with a two week interval between tests. On one occasion, selected at random, exercise testing was preceded by the administration of dipyridamole as described below. On both occasions patients exercised to a symptom-limited end point and thallium-201 (2 mCi) was injected intravenously 45 seconds before exercise was stopped.

### *Protocol for dipyridamole-exercise testing*

At least two hours after a light breakfast the patient took 300 mg of dipyridamole (three 100 mg capsules of Persantin, Boehringer-Ingelheim) by mouth, having been informed that this unusually large dose might cause headache, mild chest discomfort, or a feeling of warmth. Forty five minutes later any symptoms were recorded, a modified 12 lead electrocardiogram was analysed, and a 19 gauge butterfly cannula was inserted into a dorsal hand vein. In the absence of severe angina or ST segment changes the patient started treadmill exercise approximately 60 minutes after dipyridamole. When severe angina or ST segment changes were produced by dipyridamole alone thallium-201 was injected at rest and this was followed immediately by a slow intravenous injection of aminophylline (125–250 mg). Thallium-201 imaging was then performed without exercise.

### *Thallium-201 imaging*

Early thallium-201 images were recorded within 20 minutes of stress testing and late images four hours after testing by means of an IGE Maxicamera 400T gamma camera with a high resolution converging collimator. Planar images were obtained in the anterior, 45° left anterior oblique, and 60° left anterior oblique projections. A total of 400 000 events was collected for each image. The data were collected and processed by a Link Systems Dyanne computer. Five discrete regions of the left ventricular myocardium—anterolateral, apical, septal, inferior, and posterolateral—were defined. Each complete series of thallium-201 images (early and late) was inspected blindly and independently by three experienced observers. The images were analysed visually with and without smoothing, and in the first instance without contrast adjustment. It was agreed beforehand that any left ventricular region in which thallium-201 activity was at any point less than 75% of the maximum pixel value in the myocardial image should be classified as abnormal. Any disagreements were resolved by combined viewing of the images; after discussion the final judgment of the radiologist (RPHW) was accepted. Myocardial to background ratios were calculated for each set of images from the early 45° left anterior oblique projection. The region showing the highest activity was compared with a background (that is, pulmonary) region that was 2 cm directly above the superior cardiac border on the computer display.

### *Coronary arteriography*

Coronary stenoses shown by selective arteriography were defined as being "important" when they produced a 90% loss of cross sectional area (equivalent to a 67% diameter loss) in a major artery. Lesions producing 50–89% cross sectional area loss were defined as "minor" and of doubtful importance; and vessels with 0–49% loss were defined as "normal".

Statistical analysis was performed by Student's paired *t* test.

## RESULTS

In 80% of cases there was complete agreement between observers. The results of thallium-201 imaging after dipyridamole-exercise stress or exercise alone are summarised in Table 1. Twenty eight patients showed regional abnormalities on both occasions, whereas six showed abnormalities only after

Table 1 *Results of thallium-201 imaging after dipyridamole-exercise or exercise testing in 38 patients with coronary disease*

| *Result* | *Dipyridamole-exercise* | *Exercise* |
|---|---|---|
| Patients with abnormal scintigrams | 34/38 (89%) | 29/38 (76%) |
| Total number of early defects | 74 | 56 |
| Total number of late defects | 20 | 28 |
| Percentage of defects showing redistribution | 73 | 50 |
| Myocardial to background ratio (mean (SD)) | 3·44 (0·57)* | 2·99 (0·51)* |

*p<0·01.

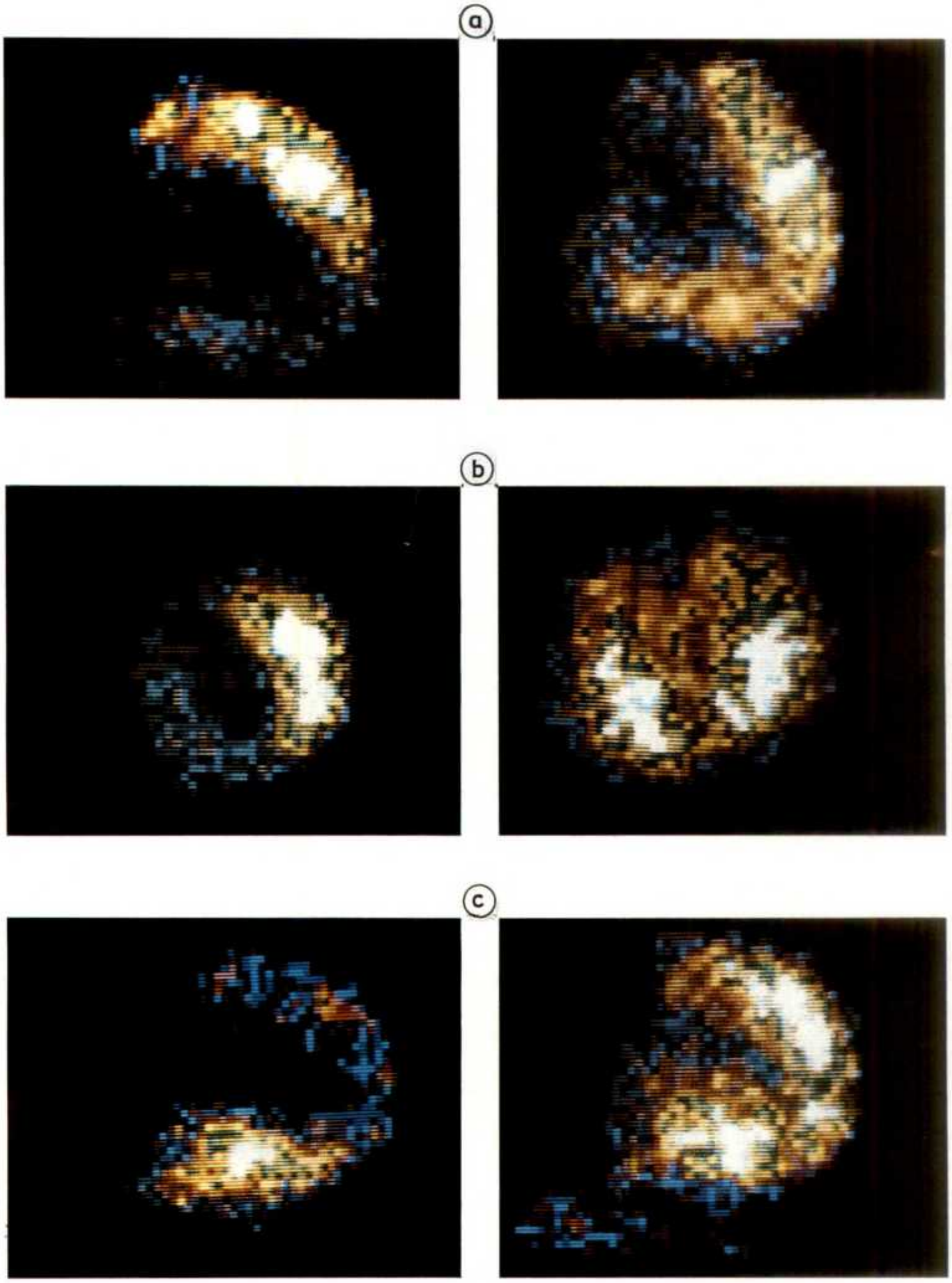

Fig. 1 *Early thallium-201 images of three patients with coronary disease in whom dipyridamole-exercise imaging (left) showed abnormal regions whereas exercise imaging (right) did not. (a) Patient 1 (right coronary occlusion): inferior defect shown in anterior projection. (b) Patient 2 (right coronary occlusion, dominant vessel) inferior and septal defects in 45° left anterior oblique projection. (c) Patient 3 (left anterior descending stenosis) anterolateral defect in anterior projection.*

Table 2 *Changes in heart rate and electrocardiogram during exercise testing (with and without dipyridamole) in 38 patients with coronary disease*

| *Variable* | *Dipyridamole-exercise* | *Exercise* |
|---|---|---|
| Maximum heart rate (beats per minute) (mean (SD)) | 119 (22)* | 126 (23)* |
| Maximum ST segment depression (mm) (mean (SD)) | 1·7 (1·0) | 1·7 (1·0) |
| Patients showing > 1 mm ST segment depression | 32/38 (84%) | 29/38 (76%) |
| Combined sensitivity of thallium-201 and ECG | 38/38 (100%) | 36/38 (95%) |

*$p < 0·05$
ECG, electrocardiogram.

dipyridamole-exercise stress and one only after exercise stress (Fig. 1). Hence dipyridamole-exercise imaging had a sensitivity of 89% for detecting coronary disease and exercise imaging had a sensitivity of 76%. Considerably more abnormal regions were detected in the early images of the whole group after dipyridamole-exercise testing than after exercise imaging, whereas fewer were present in the late images; hence dipyridamole-exercise imaging was associated with a greater degree of thallium-201 redistribution than was exercise imaging. The visual quality of the thallium-201 images, as assessed quantitatively by their myocardial to background ratios, was significantly better after dipyridamole-exercise testing.

The changes observed in heart rate and the electrocardiogram during the two exercise tests (with and without dipyridamole) are shown in Table 2. Although a significantly lower heart rate was achieved in the presence of dipyridamole, mean ST segment depression was the same as after exercise alone. Three patients who did not show ischaemic ST depression during exercise alone did so in the presence of dipyridamole, while in no patient did dipyridamole prevent the development of ST segment depression. Hence the sensitivity of the exercise electrocardiogram for demonstrating coronary disease by ST segment depression was also increased—from 76% to 84%—by the addition of dipyridamole.

When the results of thallium-201 stress imaging with dipyridamole were combined with the results of exercise electrocardiography the sensitivity was 100%. The combination of exercise electrocardiography and exercise thallium-201 imaging gave a sensitivity of 95%.

Two patients developed persistent angina with ST segment depression after dipyridamole alone and so did not proceed to the exercise phase. Both were given intravenous aminophylline, and both showed two regional abnormalities on early imaging with redistribution at four hours. Three other patients experienced mild short lived angina without ST segment depression after dipyridamole and were able to proceed to the exercise phase.

## Section 2: determination of the sensitivity and specificity of dipyridamole-exercise thallium-201 imaging

### PATIENTS AND METHODS

We added a further 49 patients who had undergone both dipyridamole-exercise imaging and coronary arteriography not more than six months apart to the 38 patients described in section 1. Exercise electrocardiography in these 49 patients had given a result which was either indeterminate or which had conflicted with the patient's history. All these patients met the first two selection criteria outlined in section 1 and had undergone dipyridamole-exercise imaging either to aid diagnosis or to evaluate the importance of minor coronary stenoses on angiography.

Thallium-201 images were analysed by two experienced observers (PRW and RPHW) using the method described in section 1.

Table 3 *Results of dipyridamole-exercise imaging and coronary arteriography in 87 patients*

| *Coronary arteriograms* | *Thallium-201 imaging* | |
|---|---|---|
| | *Normal* | *Abnormal* |
| Coronary disease demonstrated or presumed (n = 57) | 7 | 50 |
| Coronary disease not demonstrated (n = 25) | 23 | 2 |
| Minor coronary lesion present (n = 5) | 3 | 2 |

$$\text{Sensitivity} = \frac{\text{True positives}}{\text{true positives} + \text{false negatives}} \times 100$$

$$= \frac{50}{50+7} \times 100 = 87\%$$

$$\text{Specificity} = \frac{\text{True negatives}}{\text{true negatives} + \text{false positives}} \times 100$$

$$= \frac{23}{23+2} \times 100 = 92\%$$

Predictive accuracy of a positive result =

$$\frac{\text{Number of diseased patients with positive result}}{\text{all patients with positive result}} \times 100$$

$$= \frac{50}{52} \times 100 = 92\%$$

Predictive accuracy of a negative result =

$$\frac{\text{Number of disease-free patients with a negative result}}{\text{all patients with a negative result}} \times 100$$

$$= \frac{23}{30} \times 100 = 76\%$$

RESULTS

The scintigraphic and angiographic findings are summarised in Table 3, with calculations of sensitivity, specificity, and predictive accuracy. Two patients with no coronary disease had a false positive scintigram—one had severe mitral regurgitation and gross electrocardiographic abnormalities, while in the other patient, who was shown to have a mild dilated cardiomyopathy, no dipyridamole could be detected in the plasma; hence it may be assumed that standard exercise imaging would also have produced a positive result in this patient. The five patients with coronary lesions of doubtful importance were excluded from the calculations.

### Section 3: determination of optimal interval from dipyridamole to exercise testing—measurement of plasma concentrations

Sixteen patients undergoing dipyridamole-exercise testing agreed to serial venous blood sampling via an indwelling cannula at the times shown in Fig. 2. In one patient no dipyridamole could be detected in any sample and his results were excluded.

Mean dipyridamole concentration reached a peak 60 minutes after ingestion, although values that were almost as high were measured at 40, 80, 100, and 120 minutes after. At 300 minutes (when the redistribution images were being recorded) the mean concentration had fallen to 26% of the peak value.

Individually, 11 patients showed evidence of rapid absorption, whereas in three patients absorption was apparently much slower with peak values not being reached until after 120 minutes (Fig. 3).

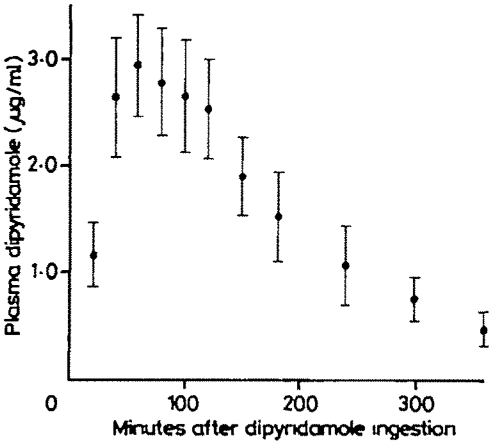

Fig. 2 *Rate of clearance of 300 mg dipyridamole in 15 patients. Values are mean (SEM)*

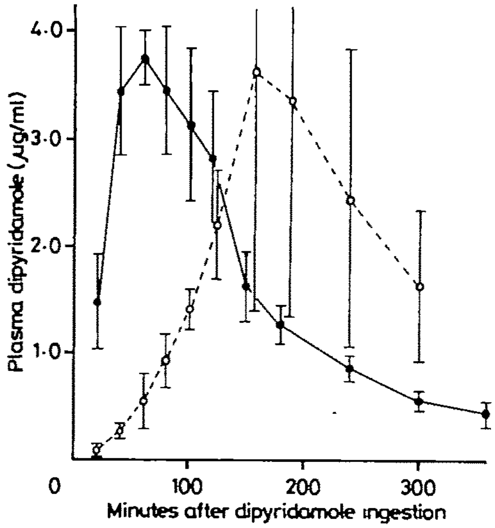

Fig. 3 *Rate of clearance of dipyridamole in 11 early absorbers (●——●) and three late absorbers (○---○). Values are mean (SEM).*

One patient (not included in Fig. 3) apparently absorbed very little dipyridamole, since his peak plasma concentration was only 0·69 μg per ml.

## Discussion

RATIONALE OF DIPYRIDAMOLE-EXERCISE TESTING

These studies have demonstrated that pharmacological coronary vasodilatation with dipyridamole superimposed on exercise stress can result in an abnormal scintigram in patients with false negative scintigrams after exercise alone. Two actions of dipyridamole may be responsible. Firstly, dipyridamole is a potent coronary arterial dilatator that acts selectively on the coronary resistance bed.[14] When injected intravenously at maximal exercise, dipyridamole produces an increase in coronary flow greater than that produced by exercise alone.[15] Intravenous dipyridamole combined with isometric handgrip exercise produces a greater increase in coronary flow than does either type of intervention alone, with the levels of flow (3 3 times the baseline values) exceeding any previously reported for the human coronary circulation.[16] Since dynamic exercise is associated with a greater increase in coronary flow than is isometric exercise[17] it is probable that dipyridamole-exercise stress increases coronary flow to an equal or even greater degree than dipyridamole combined with isometric handgrip.

The amount of thallium-201 entering myocardial cells is determined not only by coronary flow but also by how much dipyridamole is extracted—that is the extraction fraction.[18] When coronary flow is increased out of proportion to oxygen consumption, as occurs during dipyridamole induced vasodilatation,[16 18] the extraction fraction falls. Dynamic exercise on the other hand increases oxygen consumption and hence thallium-201 extraction; however, in regions in which myocardial ischaemia occurs the ability to extract thallium-201 is reduced.[18] In the present studies as in others[13 19] dipyridamole infrequently caused myocardial ischaemia; in contrast exercise consistently produced angina or ST segment depression or both. In theory the combined stress of dipyridamole and exercise should therefore maximise regional differences in thallium-201 distribution in patients with coronary disease by the differing effects of both interventions on the delivery and extraction of the radionuclide.

A second property of dipyridamole is its undisputed ability to produce myocardial ischaemia in patients with coronary disease.[19-21] Although patients with easily induced myocardial ischaemia were excluded from the present study, two patients developed angina after dipyridamole which was severe enough to require reversal by aminophylline. Five other patients either experienced mild angina after dipyridamole or demonstrated evidence of ischaemia considerably earlier in their exercise test. Two mechanisms may be responsible for the production of ischaemia: firstly, perfusion of the subendocardium may fall when flow across a stenosis of the nutrient artery is increased by, for example, vasodilatation.[22] Secondly, dilatation of resistance vessels in well perfused regions may produce steal from regions which are dependent on a collateral circulation.[23 24] There were 11 patients in whom dipyridamole undoubtedly produced myocardial ischaemia or was essential for the production of an abnormal scintigram; four of seven in whom angiography was performed were shown to have collateral dependent regions of viable myocardium.

The extent to which each of these two properties of dipyridamole was responsible for the improved sensitivity of dipyridamole-exercise imaging is uncertain. If, as seems probable, thallium-201 uptake by the lungs is not significantly affected by dipyridamole,[20] then the increased myocardial to background ratio observed with dipyridamole-exercise testing, which was responsible for the improved visual quality of the images, may be presumed to result primarily from increased myocardial blood flow. The finding that in four of the six patients in whom only dipyridamole-exercise imaging was abnormal the myocardial to background ratio was not enhanced suggests, however, that the production of ischaemia by dipyridamole must also play an important role.

### SENSITIVITY AND SPECIFICITY OF THALLIUM-201 IMAGING

The overall sensitivity for coronary disease of dipyridamole-exercise scintigraphy (the true-positive rate) was 87%; this was 13% better than the sensitivity of the standard exercise imaging. Others have reported a sensitivity of between 67%[19] and 95%[8] with exercise imaging and of between 67%[19] and 93%[25] with intravenous dipyridamole imaging. The overall sensitivity of exercise imaging was 82% in 1077 patients who had this test from 1976 to 1979[26]; however, these patients were unselected as regards disease severity, and many had previous myocardial infarction. Patient characteristics which tend to increase the sensitivity of thallium-201 imaging include previous myocardial infarction,[27] impaired left ventricular function,[13] severe coronary disease,[3 7] and an ineffective collateral circulation[28]; while the method of image interpretation (visual or quantitative) and the criteria used to define abnormality are also important determinants of sensitivity. In the present studies patients with previous infarction, poor left ventricular function, and severe coronary disease—the correlate of an early positive exercise test[29]—were excluded; while the criterion for abnormality (that is a $\geqslant 25\%$ deficiency of thallium-201 activity) was relatively strict and the method of interpretation was visual. Hence in a less carefully selected population and using a more refined method of interpretation an even higher sensitivity could no doubt have been achieved. It should be stressed, however, that any figure quoted for the sensitivity of a test is meaningful only when derived by studying the population in which the test will find clinical application—that is in symptomatic patients with conflicting or indeterminate exercise electrocardiograms.[3 5 6]

Dipyridamole-exercise imaging achieved a specificity (true-negative rate) of 92% in 25 patients without important coronary disease. False positive results, of which there were two, occurred only in patients with other cardiac lesions who were therefore likely to show scintigraphic abnormalities.[30] No patient with a normal heart had an abnormal scintigram. In the cumulative data referred to above[26] the overall specificity of exercise thallium-201 imaging in symptomatic patients was 90%. In individual studies the estimates of specificity, which have ranged from 67%[13] to 100%,[3] have often been based upon very small patient numbers. As with test sensitivity, patient selection is all important in the determination of specificity. The present study also shows that the inclusion of subjects who have other important cardiac lesions in a population with no coronary disease reduces the specificity of the test being evaluated. Again, both the criteria by which normality is defined and the method of image interpretation will further influence specificity. When visual analysis has been used the criterion for an abnormal region has been a reduction of between 15%[3] and 50%[4 7] of peak myocardial activity; while in many studies no criteria were defined.[5 13 19] Francisco *et al* were able to improve their specificity of 67% obtained with a computer enhanced visual or tomographic analysis to 96% by the use of a quantitative tomographic method.[13] In the present study the criterion for abnormality of a relative reduction in thallium-201 activity of at least 25% as assessed by computer assisted visual analysis was associated with an 80% inter-observer agreement and with high values for both sensitivity and specificity. This criterion is therefore recommended for the routine interpretation of dipyridamole-exercise images.

## IMPORTANCE OF THE ELECTROCARDIOGRAM

Proper assessment of the result of a dipyridamole-exercise test should include analysis of both the scintigram and the exercise electrocardiogram.[2] Comparison of the electrocardiogram recorded during dipyridamole-exercise or exercise testing (section 1) showed that in the presence of dipyridamole an identical average amount of ischaemic ST segment depression occurred but at a significantly lower maximal heart rate. In three patients ischaemic ST depression was seen only in the presence of dipyridamole, and this increased the sensitivity of the electrocardiogram from 76% to 84%. Others have assessed the diagnostic value of electrocardiographic changes produced by the infusion of dipyridamole, and they obtained low values for sensitivity and specificity.[31 32] If in the present study, however, an abnormal dipyridamole-exercise test result is defined as either an ischaemic ST segment response or an abnormal scintigram the sensitivity in all 57 patients with coronary disease in section 2 rises from 87% to 96%, while the predictive accuracy of a negative result (that is no scintigraphic or electrocardiographic abnormality) increases from 76% to 92%. In those two patients with coronary disease in whom no electrocardiographic or scintigraphic abnormalities were observed the maximal heart rate was less than the 85% of predicted maximal rate required for a truly negative exercise test. Thus no patient with coronary disease could be said to have had a completely negative dipyridamole-exercise test.

## DIAGNOSTIC VALUE OF REDISTRIBUTION

Redistribution of thallium-201 into regions showing defects in early images is due primarily to delayed washout of thallium-201 from ischaemic myocardium.[33] The absence of redistribution four to six hours after injection is most often due to the presence of a myocardial scar[34] but may be seen in an area of viable myocardium whose blood supply is severely compromised. In such instances redistribution may be delayed until 18–24 hours.[35] Although in earlier studies the diagnostic value of redistribution was not emphasised data from these studies[35] did suggest that "reversible" defects, that is those associated with redistribution, may be more specific indicators of coronary disease than "irreversible" defects. In the present study redistribution was seen in a greater percentage of defects detected after dipyridamole-exercise testing than in those detected after exercise alone. Moreover, all 70 reversible defects produced by dipyridamole-exercise testing were in patients with important coronary disease (predictive value = 100%), whereas three of 29 irreversible defects were in patients with no coronary disease (predictive value = 89%). Since the proper selection of patients for dipyridamole-exercise imaging excludes patients with previous myocardial infarction or easily induced ischaemia during exercise or both, a "defect" seen after dipyridamole-exercise testing which shows no redistribution should thus be interpreted with caution.

Only one patient had an abnormal scintigram on exercise testing but not on dipyridamole-exercise testing. This patient's oxygen consumption and the severity of myocardial ischaemia, as judged by maximal heart rate and ST segment depression recorded during exercise, were virtually identical on both occasions. Coronary arteriography showed a single 90% stenosis of the mid-left anterior descending coronary artery and exercise imaging demonstrated (on one projection only) an inferior defect which at four hours showed no redistribution. Since there is a fairly precise correlation between the site of scintigraphic abnormalities and the location of coronary stenosis in patients with single vessel disease,[36] both the location and the absence of redistribution cast some doubt on the importance of this defect. In contrast in those four patients in whom only dipyridamole-exercise imaging was abnormal and in whom arteriography was performed, all defects were appropriately situated and demonstrated redistribution.

The safety and low complication rate of this technique, in which two potent stresses are being imposed together on the myocardium, depend on careful patient selection—that is the exclusion of patients with easily induced myocardial ischaemia. There have been no serious complications in the 214 patients who have undergone dipyridamole-exercise thallium-201 imaging. Three per cent of patients had side effects of dipyridamole requiring reversal by aminophylline. These were prolonged angina (two patients), severe headache (two patients), and vomiting (one patient). In only three patients has the exercise phase not been possible.

Patients with coronary disease who have myocardial ischaemia within the first stage of the Bruce protocol have severe disease and a relatively poor prognosis.[29 37] Unlike patients with symptoms suggestive of ischaemic heart disease but in whom the exercise electrocardiogram is negative or equivocal, diagnosis is not difficult in such patients and they do not require thallium-201 imaging.

Dipyridamole-exercise testing appears to be better than standard exercise testing in terms of sensitivity and quality of thallium-201 imaging. In patients selected on the basis of an inconclusive exercise electrocardiogram the technique is safe, effective, and very simple.

We thank the nuclear imaging and cardiology technicians for their great contribution to this work, Dr D Davies of the University of Bath and Boehringer-Ingelheim for the dipyridamole assays and Professor K Lance Gould for his advice and encouragement.

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# Deaths from ischaemic heart disease in Belfast

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SUMMARY There were 1323 deaths due to ischaemic heart disease in Belfast from 20 July 1981 to 19 July 1982. Some 496 (37%) of these were in persons aged <70 years. By World Health Organisation criteria 247 (19%) of these deaths were classified as definite myocardial infarction and 749 (57%) as possible myocardial infarction. Dyspnoea, collapse, and typical pain were the main symptoms at the onset of the fatal attack. In hospital only 12% of deaths in persons aged <70 years and 14% of those aged ≥70 years were due to presumed primary rhythm disturbance, whereas outside hospital these proportions were 78% and 59% respectively. The median survival time was 84 minutes and was shortest in men aged <70 years (62 minutes). Outside hospital a relative was the most likely aid sought initially (70%) and the median delay time from onset of symptoms to calling for medical aid was eight minutes. Among 128 witnessed deaths in persons aged <70 years occurring outside hospital due to presumed primary rhythm disturbance the median survival time was 8·25 minutes.

Improvements in facilities available for resuscitation including public education could result in the prevention of a proportion of deaths caused by primary rhythm disturbances.

The largest single cause of mortality in developed countries today is ischaemic heart disease. Many of these deaths occur very rapidly after the onset of a coronary attack and are due to ventricular fibrillation.

We studied the circumstances of deaths from ischaemic heart disease by examining all deaths in residents of Belfast during a one year period. We investigated the various delays involved in initiating medical care in Belfast, which has two mobile coronary care units. Deaths in persons aged <70 years and in persons aged ≥70 years are described separately. Comparison with a study of deaths from ischaemic heart disease in Belfast in 1965–66 reported by McNeilly and Pemberton[1] will be described elsewhere.

## Patients and methods

### POPULATION STUDIED

Two Belfast hospitals, the Royal Victoria Hospital and the Ulster Hospital, Dundonald, provide mobile coronary care units. Access to the ordinary emergency ambulance by the general public is by means of a 999 telephone call. If the ambulance controller suspects a heart attack the call is transferred to a mobile coronary care unit. The mobile coronary care unit also accepts calls from general practitioners and former patients to a special emergency telephone number. There are about 200 general practitioners, and some 30 practices use a deputising service at night and at weekends.

The population studied (355 980) included all men and women of all ages resident in the city of Belfast and the adjacent local government district of Castlereagh. This area is conterminous with the boundaries of three health and social services districts (North and West Belfast, South Belfast, and East Belfast and Castlereagh). We investigated all deaths occurring in residents of the study area during one year from 20 July 1981 to 19 July 1982 inclusive.

### ASCERTAINMENT OF DEATHS

Several procedures were used before a death was accepted as being due to ischaemic heart disease. The first and primary source of ascertainment was the death certificates filed at the General Register Office for Northern Ireland. All deaths attributed to Inter-

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Accepted for publication 13 January 1986

national Classification of Diseases 410-414 (Ninth Revision 1975) were presumed to be due to ischaemic heart disease. We also scrutinised all certificates relating to Belfast residents dying from any cause. Deaths that were thought probably or possibly to have been due to ischaemic heart disease were provisionally included. Then these presumed ischaemic heart disease deaths were verified by other sources including records from hospitals, necropsy reports, the Coroner's Office, general practitioners, and ambulance services. In 302 instances necropsy reports were available. Thirdly, 775 home visits were made by a study doctor or social worker to the relatives of the deceased or an informant between three and eight weeks after the death. These interviews took place in order to clarify the circumstances relating to fatalities outside hospital in particular and to other items. Eye witnesses of fatal attacks that began in the street and elsewhere also were interviewed. A panel of cardiologists from the Regional Medical Cardiology Centre, Royal Victoria Hospital, assessed data relating to equivocal cases. The diagnostic criteria that were used for acute myocardial infarction were based on those set out by the World Health Organisation in 1981[2] but without the Minnesota coding of electrocardiographs. Survival times were measured from the onset of symptoms to the time of death. In accord with the World Health Organisation protocol onset was defined as the start of severe acute symptoms, excluding prodromal symptoms, with a maximum survival time of 28 days. Survival times were known within ±5% for 715 deaths. Deaths from sudden collapse without previous symptoms were assigned a survival time of four minutes unless cardiopulmonary resuscitation was carried out. The survival time could not be estimated to within ±5% in 145 deaths, 265 deaths were unwitnessed, and in 152 the fatal attack had no specific onset.

We used the $\chi^2$ test for statistical analysis. Permission for the study was given by the medical ethical committee, and visits to relatives were made only with consent from the deceased person's general practitioner. One family practice refused to participate, and seven relatives refused interview.

## Results

Scrutiny of death certificates produced 1654 deaths which were possibly due to ischaemic heart disease. Assessment of clinical and other data relating to all deaths coded as 410–414 and the possible deaths coded by other International Classification of Diseases numbers excluded 331, leaving 1323 deaths for further investigation.

### DIAGNOSIS BY WORLD HEALTH ORGANISATION CRITERIA

Some 56% of all deaths from ischaemic heart disease occurred in men aged between 35 and 95 years (mean 69 years). The other 44% were in women aged between 41 and 99 years (mean 76 years); 48% of the male deaths and 25% of the female deaths were in people aged <70 years (Table 1). In those aged <70 assessment by World Health Organisation criteria showed that 128 deaths (26%) were

Table 1 *Mortality from ischaemic heart disease over one year (1981–82) in Belfast*

| *Age group* | *Population* | | *Numbers of deaths* | | *Mortality rates/1000* | |
|---|---|---|---|---|---|---|
| | *Male* | *Female* | *Male* | *Female* | *Male* | *Female* |
| <70 yr | 156 621 | 165 026 | 351 | 145 | 2 2 | 0 9 |
| ≥70 yr | 11 502 | 22 831 | 384 | 443 | 33 | 19 |
| All ages | 168 123 | 187 857 | 735 | 588 | 4 4 | 3 1 |

Table 2 *Main symptom at the onset of the fatal attack by age and sex*

| *Symptom* | *Males* | | *Females* | |
|---|---|---|---|---|
| | *<70 yr* | *≥70 yr* | *<70 yr* | *≥70 yr* |
| Dyspnoea | 35 (13) | 90 (30) | 31 (27) | 123 (36) |
| Collapse | 93 (34) | 83 (28) | 24 (21) | 64 (18) |
| Typical pain* | 88 (32) | 72 (24) | 40 (35) | 63 (18) |
| Atypical pain† | 23 (8) | 19 (6) | 6 (5) | 21 (6) |
| Other | 36 (13) | 37 (12) | 13 (12) | 75 (22) |
| Total | 275 (100) | 301 (100) | 114 (100) | 346 (100) |

Numbers in parentheses are percentages.
*Including chest, arm, and neck pain but excluding mild pain in any site.
†Including epigastric and back pain and mild chest, arm, and neck pain.

classified as definite myocardial infarction, 306 (62%) as possible myocardial infarction, and in 62 (12%) there was insufficient evidence for classification. In those aged 70 years and above the numbers were 119 (14%), 443 (54%), and 265 (32%) respectively.

### MAIN SYMPTOM AT ONSET

We ascertained the main symptom at the onset of the fatal attack in relation to 1036 deaths. We excluded 287 deaths (107 in persons aged <70 years). The reason for most exclusions was because the fatal attack was unwitnessed. For the 275 men aged <70 years sudden collapse without prior warning was the most common main symptom and occurred in 93 (34%) (Table 2). Typical cardiac pain was almost as common (88 cases (32%)). The distribution of symptoms in females aged <70 years was significantly different from that in men aged <70 years ($\chi^2=15{\cdot}76$, $p<0{\cdot}01$). The most common symptom was typical pain (40 (35%) of 114), with dyspnoea in 31 (27%) and collapse in 24 (21%). The distribution of symptoms in men aged ≥70 years was significantly different from that in younger men ($\chi^2=25{\cdot}64$, $p<0{\cdot}001$). Dyspnoea was the most common main symptom (90 (30%) of 301 persons), with collapse in 83 (28%) and typical pain in 72 (24%). Dyspnoea was the most common symptom in females aged ≥70 years, occurring in 123 (36%) of 346. Other non-specific symptoms were common (75 cases (22%)). This distribution was significantly different from that in women aged <70 years ($\chi^2=17{\cdot}81$, $p<0{\cdot}01$) and from that in men aged ≥70 years ($\chi^2=18{\cdot}12$, $p<0{\cdot}01$).

### MODE OF DYING

Deaths from ischaemic heart disease were due mainly to pump failure or a presumed primary rhythm disturbance, of which the most frequent is known to be ventricular fibrillation (Table 3). People who collapsed suddenly were judged to have died from a primary rhythm disturbance as were those who were found dead (often in bed), unless there was some evidence of distress before death. Thirteen cases were found to have ventricular rupture at necropsy and we have included these in the "other" category. Also included in this category are those who collapsed in cardiac arrest without pre-

Table 3 *Mode of dying inside and outside hospital by age*

| *Mode of dying* | *Inside hospital* | | *Outside hospital* | |
|---|---|---|---|---|
| | *<70 yr* | *≥70 yr* | *<70 yr* | *≥70 yr* |
| Heart failure and shock | 139 (76) | 261 (71) | 34 (12) | 110 (26) |
| Presumed primary rhythm disturbance | 21 (12) | 53 (14) | 229 (78) | 259 (59) |
| Other | 20* (11) | 37† (11) | 11 (4) | 6 (1) |
| Unknown | 1 (1) | 14 (4) | 18 (6) | 64 (14) |
| Total | 181 (100) | 365 (100) | 292 (100) | 439 (100) |

Numbers in parentheses are percentages
*Including 1 death due to pulmonary embolism and 5 due to arterial embolism
†Including 3 deaths due to pulmonary embolism and 6 due to arterial embolism.

Table 4 *Survival times by age and sex*

| *Time* | *Males* | | *Females* | | *Both sexes* |
|---|---|---|---|---|---|
| | *<70 yr* | *≥70 yr* | *<70 yr* | *≥70 yr* | |
| 0–4 min | 34 (16) | 52 (24) | 12 (14) | 42 (20) | 140 (19) |
| 5–14 min | 29 (15) | 23 (11) | 14 (16) | 23 (11) | 89 (13) |
| 15–29 min | 12 (6) | 13 (6) | 6 (7) | 13 (6) | 44 (6) |
| 30–59 min | 27 (13) | 12 (6) | 9 (10) | 14 (7) | 62 (9) |
| *Total <1 hr* | 102 (50) | 100 (47) | 41 (47) | 92 (44) | 335 (47) |
| 1–<6 hr | 35 (17) | 21 (11) | 8 (9) | 14 (6) | 78 (11) |
| 6–<24 hr | 11 (5) | 27 (12) | 12 (14) | 25 (12) | 75 (10) |
| 1–<7 days | 34 (16) | 38 (18) | 12 (14) | 43 (21) | 127 (18) |
| 7–28 days | 24 (12) | 27 (12) | 14 (16) | 35 (17) | 100 (14) |
| *Total* | 206 (100) | 213 (100) | 87 (100) | 209 (100) | 715 (100) |
| Not known accurately* | 126 (38) | 159 (43) | 54 (38) | 223 (52) | 562 (44) |
| *Total* | 332 (100) | 372 (100) | 141 (100) | 432 (100) | 1277 (100) |
| Median times (min) | 62 | 90 | 90 | 340 | 84 |

Numbers in parentheses are percentages.
*Includes 265 unwitnessed, 152 with no specific onset of the attack, and 145 deaths known with accuracy greater than ±5%.

vious pump failure in whom a satisfactory electrocardiogram rhythm was continuously present or was established by immediate efficient resuscitation, but without any concomitant cardiac output. Data relating to the mode of dying were obtained for the 1277 deaths whose fatal attack occurred within the study area. A total of 546 occurred inside hospital and 731 outside hospital. Only 74 deaths (13·5%) were due to presumed primary rhythm disturbance and 400 (73%) were due to pump failure in the inside hospital group. The distribution was reversed in persons dying outside hospital where 488 deaths (67%) were judged to be due to presumed primary rhythm disturbance and 144 (20%) to pump failure $(\chi^2=476{\cdot}54, p<0{\cdot}001)$. This difference in the mode of dying was significant in those aged <70 years $(\chi^2=241{\cdot}88, p<0{\cdot}001)$ and in those aged ≥70 years $(\chi^2=247{\cdot}15, p<0{\cdot}001)$.

### SURVIVAL TIME

Seven per cent (34 of 473) of those aged <70 years and 15% (118 of 804) of those aged ≥70 had no specific onset of symptoms. In a further 410 cases (146 aged <70 years) the survival time was not known with sufficient accuracy (that is ±5%) and these were excluded from the analysis of survival times (Table 4). Some 140 persons (19%) survived for up to four minutes only. For all persons the median survival time from the onset of symptoms to death was 84 minutes. It was nearly twice as long (121 minutes) in those ≥70 compared with those <70 years of age (65 minutes). $\chi^2$ analysis of the time intervals showed that the distribution of survival times was not significantly different in men and women in both age groups or in women aged <70 years and those aged ≥70 years, but it was significantly different in men aged <70 years and those aged ≥70 years $(\chi^2=20{\cdot}79, p<0{\cdot}01)$.

### AID REQUESTED AND ASSOCIATED DELAYS

Most attacks began at home—335 (71%) in those aged <70 years and 538 (67%) in those aged ≥70 years among the 1277 deaths occurring inside the study area.

For the age group <70 years the attack began in the street in 36 (8%), at work in 23 (5%), at a place of public entertainment in 11 (2%), in hospital for non-cardiac reasons in 57 (12%), or in other places in 11 (2%). For the age group ≥70 years the onset was in the street for 32 (4%), at work in one, in places of public entertainment in three, in general practitioners' surgeries in two; a large number (215 (16%)) were already in hospital, mainly in geriatric wards; and 69 (9%) were in nursing homes or old people's homes. The distribution of deaths by place of onset is not quite the same as the distribution of deaths by place of death. Some 230 (79%) of the 292 deaths outside hospital that occurred in persons aged <70 years and 361 (82%) of the 439 deaths in persons aged ≥70 years took place at home. Considering all ages there were 42 deaths in the street, 18 at work, 18 in places of public entertainment, four in general practitioners' surgeries, and 55 in nursing and old people's homes. The respective figures for the age group <70 years are 20, 17, nine, one, and six deaths. There were 13 deaths during transit to hospital, nine occurring in persons aged <70 years.

Some form of aid was sought by 809 (77%) persons out of the 1062 persons with onset of attack outside hospital and within the study area. In 564 (70%) cases a relative was summoned first, a lay person in 124 (15%), and another person, usually a

Table 5 *Median delay times for requesting medical care*

| *Delay time* | *<70 yr* | | *≥70 yr* | |
|---|---|---|---|---|
| | *No of persons* | *Time (min)* | *No of persons* | *Time (min)* |
| Onset of fatal attack to call for first (lay) aid | 253 | 11 | 306 | 11 |
| Call for first aid to call for medical aid | 258 | 5 | 283 | 5 |
| Onset to call for medical aid | 228 | 10 | 229 | 8 |
| Onset to call for MCCU | 107 | 15 | 62 | 15 |
| Onset to call for OA | 120 | 7 | 132 | 21 |
| Call for GP to arrival of GP | 70 | 15 | 157 | 30 |
| Call for DD to arrival of DD | 24 | 21 | 54 | 20 |
| Call for MCCU to arrival of MCCU | 116 | 10 | 73 | 10 |
| Call for OA to arrival of OA | 144 | 8 | 211 | 11 |
| Onset of fatal attack to arrival of MCCU or hospital ward/CCU care | 105 | 90 | 102 | 195 |

MCCU, mobile coronary care unit; GP, general practitioner; OA, ordinary ambulance, DD, deputising doctor; CCU, coronary care unit.
Persons already in hospital at onset of fatal attack are excluded.
Data presented for delay times known with accuracy of ±5%

neighbour or staff at a nursing or old people's home in 97 (12%). The remaining 24 (3%) sought medical aid themselves. Medical aid was sought for 297 (72%) of those aged <70 years. The aid requested was the ordinary ambulance for 87 (29%), the general practitioner for 86 (29%), the mobile coronary care unit for 77 (26%), the deputising doctor for 27 (9%); nine (3%) came direct to hospital accident and emergency departments, and 11 (4%) sought other forms of medical aid. For persons aged ≥70 years 214 (51%) requested their general practitioner, 82 (20%) the ordinary ambulance, 64 (15%) a deputising doctor, 48 (11%) the mobile coronary care unit, five came direct to hospital accident and emergency departments, and four sought other medical aid.

Table 5 summarises the median delay times where they were known within an accuracy of ±5%. Both the median delay time in calling for first (lay) aid (1 minute) and the delay in calling for medical aid (10 minutes in those aged <70 years and eight minutes in those aged ≥70 years) are very short. The median delay times for the arrival of medical aid are also very short, varying from eight minutes for the ordinary ambulance in the case of younger people to 30 minutes for the general practitioner in the case of older people.

### WITNESSED DEATHS DUE TO PRESUMED PRIMARY RHYTHM DISTURBANCE OUTSIDE HOSPITAL

We identified a subgroup of 128 deaths that occurred outside hospital in those aged <70 years where death was witnessed by a person aged 13–64 years and was due to presumed primary rhythm disturbance (Figure). There were 97 males (76%) and 31 females. Some 18 (14%) had definite myocardial infarction, 92 (72%) had possible myocardial infarction, and 18 (14%) had insufficient evidence to make a classification. Only 61 (49%) had known previous ischaemic heart disease, 14 (11%) had possible previous ischaemic heart disease (not diagnosed) or very recent angina, and 53 (41%) had no previous history. The majority (80 (62%)) presented with sudden collapse and the median survival time was 8·25 minutes. A mobile coronary care unit attended 54 persons (42%) either as the first medical aid (40) or as back up to other services (14). Cardiopulmonary resuscitation had been initiated by bystanders in 55 cases (43%) but was apparently efficient in nine cases only. The majority (73 (57%)) had no cardiopulmonary resuscitation carried out before the arrival of medical aid although nearly all cases had already collapsed (115 (96%)) of 120 cases where medical aid was sought).

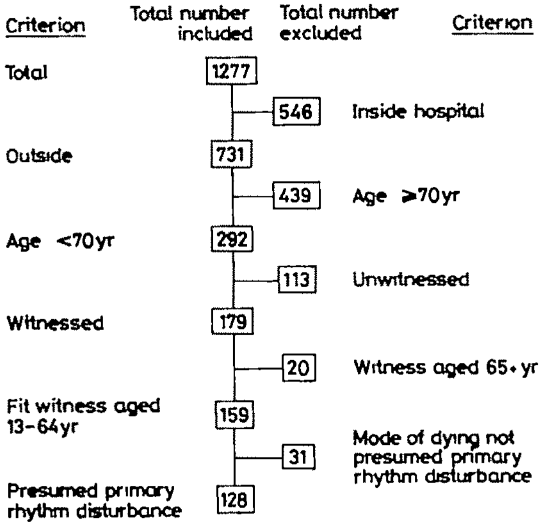

Figure *Ascertainment of the number of potentially preventable deaths.*

## Discussion

The present study of deaths in Belfast illustrates the difficulties of providing appropriate medical care because of the circumstances surrounding fatal attacks of ischaemic heart disease. The median survival time was only 84 minutes and was shorter (65 minutes) in persons aged <70 years. The great majority (83%) of fatal attacks began outside hospital and of these 82% began in the person's home. A relative was therefore the most likely (70%) first source of aid. Although 67% of deaths outside hospital were due to a presumed primary rhythm disturbance, and were potentially treatable, many persons had no symptoms before collapse or death to alert their relatives. The classic symptom of severe crushing central chest pain radiating to the arms or neck occurred only in 33% of persons aged <70 years and 21% of those aged ≥70 years. Sudden collapse without warning was the most common (34%) presenting symptom in men aged <70 years. Once relatives or witnesses were alerted to the person's attack, the delay in calling for medical aid was very short, a median time of five minutes, and the delay times in medical aid arriving were also very short (median times ranging from eight minutes to 30 minutes).

We identified a subgroup of 128 deaths occurring outside hospital in persons aged <70 years in which death was witnessed and was due to a presumed primary rhythm disturbance. They represent 26% of all deaths in this age group. Sudden collapse was the most common presentation (62%). Wennerblom reported that 52% of witnessed deaths due to ischaemic heart disease occurring outside hospital in persons aged <75 years in Gothenburg presented with cardiac arrest.[3] Some 53% of men and 49% of women aged <65 years whose death was witnessed outside hospital in Helsinki presented with cardiac arrest.[4] Liberthson *et al*, reporting on sudden cardiac deaths outside hospital, stated that 50% died instantly and a further 25% died within 30 minutes.[5] The median survival time among the 128 deaths we identified was only 8·25 minutes and 70% died within 30 minutes. It is unlikely that any system of medical care which does not provide resuscitation services outside hospital can reduce mortality in this group which includes many preventable deaths.

During the study period eight persons aged <70 years were successfully resuscitated from out of hospital cardiac arrest present before a mobile coronary care unit had arrived and they survived for at least one year. Possible strategies for dealing more effectively with this problem include training the adult population in the technique of cardiopulmonary resuscitation to enable some of those developing ventricular fibrillation at the onset of their attack to survive until the arrival of a medical team with a defibrillator. Since, however, it is common experience in the hospital coronary care unit that extremely rapid defibrillation improves survival, the provision of suitable defibrillators to selected members of the public, for example to relatives of persons known to be at risk, should be considered. In our subgroup about half of these persons could have been identified because they had known ischaemic heart disease. Since a substantial number of persons are attended by general practitioners, deputising doctors, and ordinary ambulance staff, these groups should be equipped with defibrillators and trained in their use.

We thank the Registrar General for Northern Ireland, staff of the General Register Office, the Coroner's Office for Belfast, and many colleagues for their assistance with this study. Dr W McIlwaine was the holder of a Royal Victoria Hospital Research Fellowship and the work was supported by the Heart Trust Fund.

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*Br Heart J* 1986; 55: 336–43

# Continuous ambulatory pulmonary artery pressure monitoring

## *A new method using a transducer tipped catheter and a simple recording system*

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SUMMARY A transducer tipped catheter and simple recording system were used for the continuous measurement of ambulatory pulmonary artery pressure. The pulmonary artery pressure was recorded on a miniaturised tape recorder and replayed via an optical writer. Pulmonary arterial systolic and diastolic pressures can be analysed on a beat to beat basis. Continuous ambulatory monitoring was performed for a total 288 hours in 13 patients who were undergoing routine investigation for coronary artery disease. There was less than 1% zero drift and 0·25% linearity error per full scale pressure. The frequency response of the entire system was flat to 8 Hz with a linear phase delay. The transducer tipped catheter and a conventional fluid-filled system were used to measure left ventricular and pulmonary artery end diastolic pressures in eight patients. The correlation between the results obtained by the two methods was excellent. This method could be used at any centre equipped for ambulatory electrocardiographic monitoring.

The measurement of pulmonary artery end diastolic pressure provides an accurate assessment of left ventricular end diastolic pressure in the absence of pulmonary vascular disease and mitral stenosis.[1-3] Until recently recording of pulmonary haemodynamics in man using fluid filled systems was restricted because the equipment was not portable.[1 4 5] Lately, ambulatory pulmonary artery pressure monitoring with fluid filled and transducer tipped catheters in unrestricted subjects has been described. A miniaturised tape recorder was used with the fluid filled catheter and a solid state system was used with the transducer tipped catheter. Data analysis was computerised in both studies.[6 7]

Fluid filled catheters have many drawbacks, such as difficulty with the localisation of the zero reference point, the requirement for anticoagulation, and the need to use filtering for data retrieval.[8] In the previous study in which a transducer tipped catheter was used pressure results were avaraged every thirty seconds.[7]

We describe a simple method for continuous ambulatory pulmonary artery pressure monitoring by means of a transducer tipped catheter and widely available ambulatory monitoring recording equipment.

## Patients and methods

### PATIENTS

Thirteen patients (12 male and one female, mean age 52·5 (range 33–70) years) with clinical and electrocardiographic evidence of coronary artery disease were studied while undergoing routine cardiac catheterisation. In eight patients we simultaneously recorded measurements from transducer tipped and fluid filled catheters. The study was approved by the ethics committee and patients gave their informed and written consent.

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Accepted for publication 7 January 1986

### CATHETER SYSTEM

We used a polyurethane 6 French NIH type catheter (Gaeltec) with a miniature strain gauge transducer (10 mm long and 2 mm in diameter) mounted on the tip. The sterile catheter was immersed in saline for at least one hour to stabilise the silicone elastomer covering the transducer.

The catheter was placed in a moist sterile calibration tube. The zero potentiometer on the control box was adjusted to an output of zero mV. The gain potentiometer was adjusted to an output of 40 mV for a pressure of 80 mm Hg. It was necessary to calibrate each transducer before use because the sensitivity of catheters varied by 5%. The outputs at different pressures were measured on a digital voltmeter and recorded on the Oxford Medilog I tape recorder. Simultaneous recordings were obtained on an oscilloscope and dry silver paper via a Hewlett Packard bioelectric amplifier in the catheter laboratory.

### IN VIVO VALIDATION

The catheter was introduced percutaneously via the right subclavian vein to a proximal pulmonary artery under fluoroscopy. A conventional fluid filled catheter (7 Cournand) was introduced via the right femoral vein and passed into the pulmonary artery in a comparable position. An 8 French pigtail catheter was introduced via the right femoral artery to provide simultaneous recordings of transducer tipped pulmonary artery pressure, fluid filled pulmonary artery pressure, and left ventricular end diastolic pressure. Changes on deep inspiration, expiration, and during a Valsalva manoeuvre were recorded.

After routine coronary angiography the femoral catheters were removed. A 24 h ambulatory recording of the pulmonary arterial waveform, frequency modulated electrocardiogram (leads CM2 and CM5), and amplitude modulated electrocardiogram (lead CM5) was obtained. After 24 h the pulmonary artery line was removed and zero drift was measured on the digital volt meter. The catheter was then recalibrated after blood had been washed off the silicone membrane covering the transducer.

### RECORDING

The transducer was driven and demodulated by an electrically isolated Gaeltec preamplifier. The pulmonary artery pressure was recorded on an Oxford Medilog I multichannel miniature tape recorder which was modified by the insertion of an AM4 pressure module. The modulation was adjusted to a maximum applied pressure of 80 mm Hg. Higher pressures could be recorded but because errors of measurement are quoted on a % full scale basis, the lower the full scale maximum, the more accurate the recording. Up to 25 h of pulmonary artery pressure could be recorded at 2 mm/s on C120 cassettes. An amplitude modulated electrocardiogram can be recorded via this box.

### FREQUENCY MODULATED ELECTROCARDIOGRAM

Faithful recordings of ST segments were obtained by means of a frequency modulated Oxford Medilog II recording and playback system (frequency response 0 05–40 Hz −3 dB down). Two pairs of bipolar electrodes were applied precordially to record leads CM2 and CM5 and a 24 h two channel ambulatory recording of the electrocardiogram was obtained. An event marker was linked to both the frequency modulated electrocardiogram and pulmonary artery trace. The system therefore permitted synchronous ambulatory recording of both pulmonary artery pressure and the frequency modulated electrocardiogram.

### PLAYBACK

The tapes were played at 60 times recorded time. The pulmonary artery pressure was demodulated by an Oxford Instruments PM3 unit and the amplitude modulated electrocardiogram was played via a PD2 direct replay amplifier. Both were played via a PB2 playback unit on to a multichannel ultraviolet optical writer. The frequency modulated electrocardiogram was demodulated via a PB4 unit on to the optical writer and was also played on an Oxford Medilog II MA20 scanner.

### OPTICAL WRITER

An ultraviolet SE Laboratories 6008 oscillograph was used. This has a variable playback speed of 25

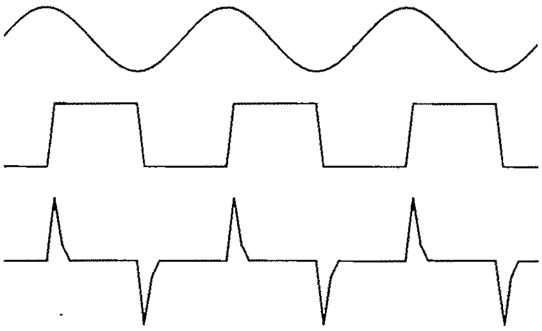

Fig. 1 *Simultaneous sine wave and differentiated square wave recordings. Top, sine wave; middle, square wave; bottom, differentiated square wave. The relation of the differentiated square wave to a given point in the sine wave was measured at different frequencies to assess phase delay*

mm per minute to 4000 mm per second. The galvanometers have a frequency response up to 1 KHz. A speed of 1500 mm per second represents a real time recorded speed of 25 mm per second that of a standard electrocardiogram. The pulmonary artery pressure and amplitude modulated electrocardiogram were replayed simultaneously. Event marks on the pulmonary artery trace and the frequency modulated electrocardiogram were used to line up the recordings.

## FREQUENCY RESPONSE OF THE MEASURING SYSTEM

The recording system can be separated into four components: (*a*) catheter and preamplifier; (*b*) Oxford Medilog AM4 recording system; (*c*) Oxford Medilog PB2 playback system; (*d*) display/writeout system.

### *Catheter and preamplifier (direct recording)*

The frequency response of the catheter and preamplifier was measured by a "pop" test.[9] The catheter was enclosed in a rigid container with an opening for a three way tap. This was connected to a syringe which had a small hole in it. The system was put under pressure, either by pushing or pulling the syringe, with the hole occluded. When the occlusion was removed, a step pressure was applied. Its response was estimated by the degree of overshoot (ringing) of the recorded pressure and the frequency of oscillation of the ringing.

### *Recording and playback systems*

*Amplitude response* was measured by the standard method of applying sine waves of constant amplitude but varying frequencies to the system and measuring the output amplitude.

*Phase response* refers to the phase angle of the output signal after it has passed though the system in relation to the input signal. If a 1 Hz signal is delayed by 0·1 seconds, it has suffered a phase shift (delay) of 36 degrees (1/10 of cycle). Similarly, if a 5 Hz signal is delayed by 0·1 second it has a phase delay of 180 degrees, because 0·1 second is half of the cycle length of 0·2 seconds. In general the delay (d) is related to the phase (p) (where (p) is a function of the frequency (f)) by the equation of $p = d \times f \times 360$ degrees. In order to represent faithfully a signal, certain frequency components must not be delayed with respect to others because this will lead to signal distortion.[10] Therefore, the delay (d) must remain constant. If (d) is a constant, then

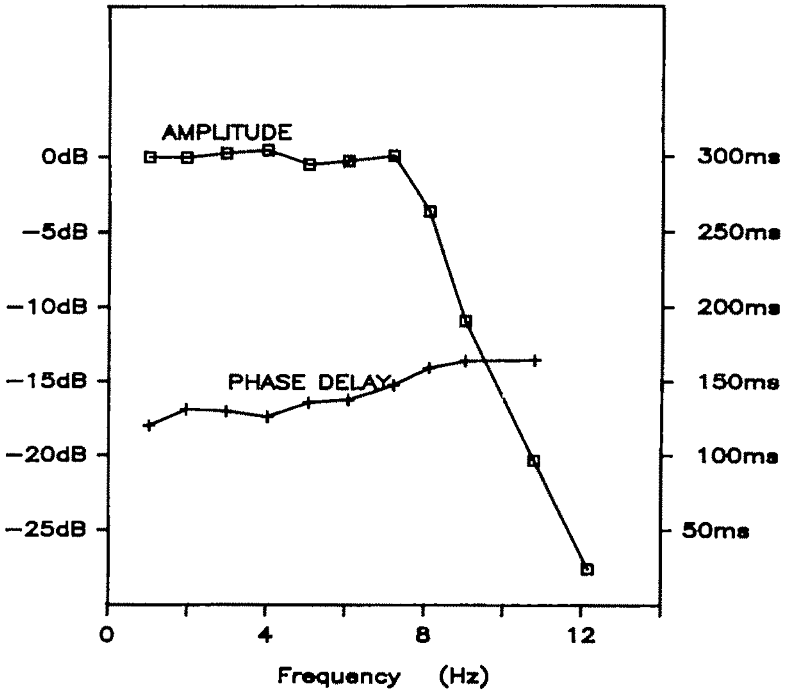

Fig. 2 *Amplitude response (dB) and phase delay (ms) with increasing frequency. The amplitude response was flat to 8 Hz with a linear phase response over the same frequency range.*

the phase delay (p) must be a linear function of frequency (f) and therefore p/f=constant. Measurement of phase response is difficult because a reference to the original phase of the signal must be preserved for comparison with the condition signal. A new method was used to measure the phase response of the recording and playback systems. A sine wave of varying frequency was recorded as the pressure channel 1 (Fig. 1). A simultaneous phase-locked synchronised square wave was electronically differentiated (time constant 5 ms), attenuated, and then recorded as a series of positive and negative spikes on channel 2 (the electrocardiogram channel). These spikes were identical in shape at all input frequencies and were thus recorded identically, giving a time reference for the phase delay measurements.

### *Display/writeout system*

In practice the display/writeout system will only impose frequency response limitations if a hot pen recorder is used. In the present study all recordings were made on an SE Laboratories ultraviolet recorder, which has a frequency response far in excess (>1 kHz) of that required for pulmonary artery pressure monitoring.

*Fourier analysis*—Signals were displayed and averaged on a Gould 1425 digital storage oscilloscope. The oscilloscope had an eight bit accuracy which is equivalent to −50 dB. Data were analysed off line on a Hewlett Packard 150B microcomputer and a customised fast Fourier transform (FFT) programme. Data were obtained (*a*) directly from the Gaeltec preamplifier; (*b*) from a fluid filled pulmonary artery catheter system; and (*c*) from the recordings played via the replay unit. Waveform configuration and harmonic content were analysed from each source at varying heart rates.

### STATISTICS

Wilcoxon's rank sum test was used for statistical analysis.

## Results

### EVALUATION OF THE CATHETER RECORDING-PLAYBACK SYSTEM

When the catheter pop test was applied to the Gael-

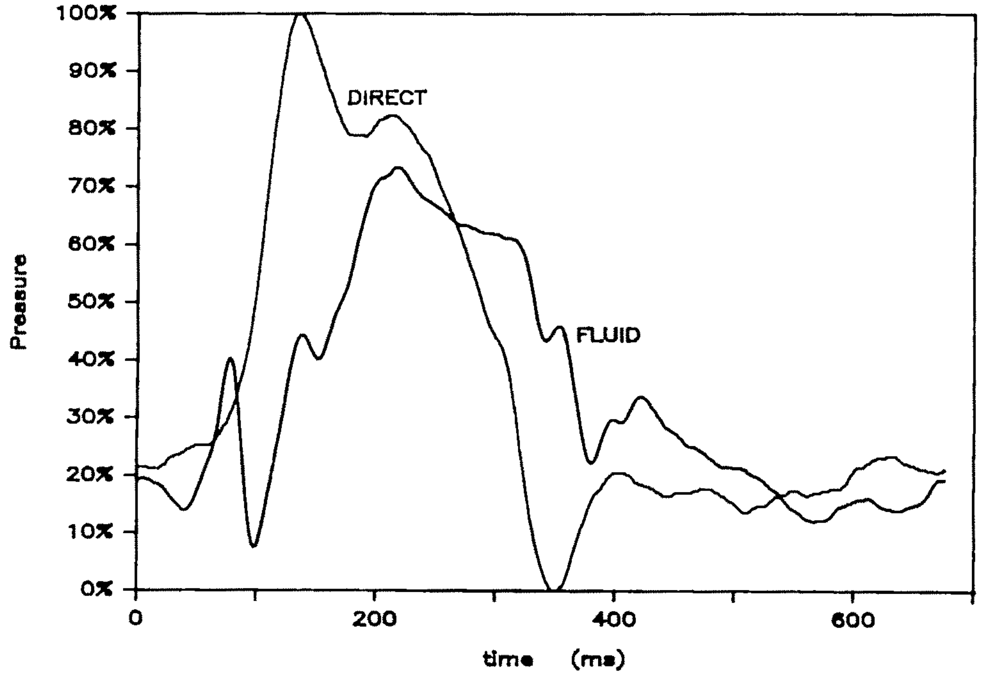

Fig. 3 *Simultaneous recordings of transducer tipped and fluid filled pulmonary artery pressure waveform at a constant heart rate of 90 beats per minute. The direct recording is the pressure from the trandsucer tipped catheter and Gaeltec preamplifier. Pressure is expressed as a percentage of the maximum transducer tipped pulmonary artery pressure.*

tec catheter and preamplifier the overshoot was less than 2% of the applied pressure and the resonant frequency of the system was 285 Hz. Thus there is little or no effect on the frequency response of the overall system due to losses in this element.

The amplitude response of the entire system was flat to 8 Hz. The phase response was linear over the same frequency range (Fig. 2). The phase delay at 8 Hz differed from that at 1 Hz by less than 30 ms. Hence, phase distortion was insignificant up to 8 Hz.

Simultaneous recording of direct transducer tipped and fluid filled pulmonary artery pressure showed no difference in the end diastolic pressures, but fluid filled systolic pressure is 25% less than the Gaeltec systolic pressure and the fluid filled curve is shifted to the right, the recording being delayed by the presence of connecting tubing (Fig. 3).

*Fast Fourier transform*—The power spectra from direct recordings of transducer tipped and fluid filled catheters were compared together with the amplitude modulated recording (Fig. 4). These were obtained at a constant heart rate of 90 beats per minute. At low frequencies, in the physiological range, the fluid filled system attenuates the amplitude of the frequency content and this affects even the first harmonic. Absolute power is expressed in decibels where 0 dB is equivalent to 1 mm Hg, 20 dB to 10 mm Hg, and 40 dB to 100 mm Hg. Flattening out of the curve occurs at −30 dB. Within the physiological range the power spectrum of the transducer tipped catheter pressure waveform on the Oxford recorder did not differ greatly from the direct recording. Measurements of harmonic power were obtained at different heart rates. At 70 beats per minute 90% of the harmonic power is expressed below 8 Hz, at 90 beats per minute this is reduced to 80%, and at 150 beats per minute it is 70%. Waveform distortion will increase with increasing heart rate, but this is more intense in higher frequencies and therefore systolic rather than diastolic pressures are distorted. At 150 beats per minute there was a slight increase in higher frequency components.

*Signal/noise ratio*—The recorded noise level was less than −50 dB assessed by amplitude.

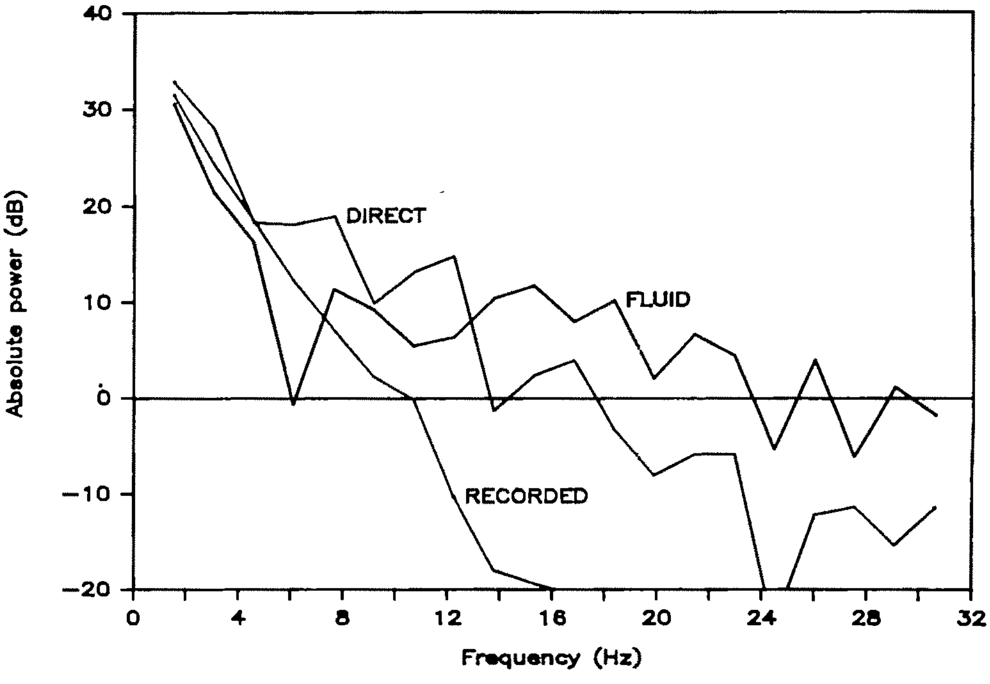

Fig. 4 *Fast Fourier transform analysis of direct recordings of pulmonary artery pressure by the transducer tipped and fluid filled catheters together with recordings on the Oxford Medilog system. Absolute power is expressed in decibels. (0 dB = 1 mm Hg, 20 dB = 10 mm Hg, 40 dB = 100 mm Hg). These recordings were obtained at a constant heart rate of 90 beats per minute. At low frequencies, in the physiological range, the fluid filled system attenuates the amplitude of the frequency content, and this affects even the first harmonic. The power spectrum of the transducer tipped pulmonary artery pressure waveform on the Oxford recorder did not differ greatly from the direct recording within the physiological range.*

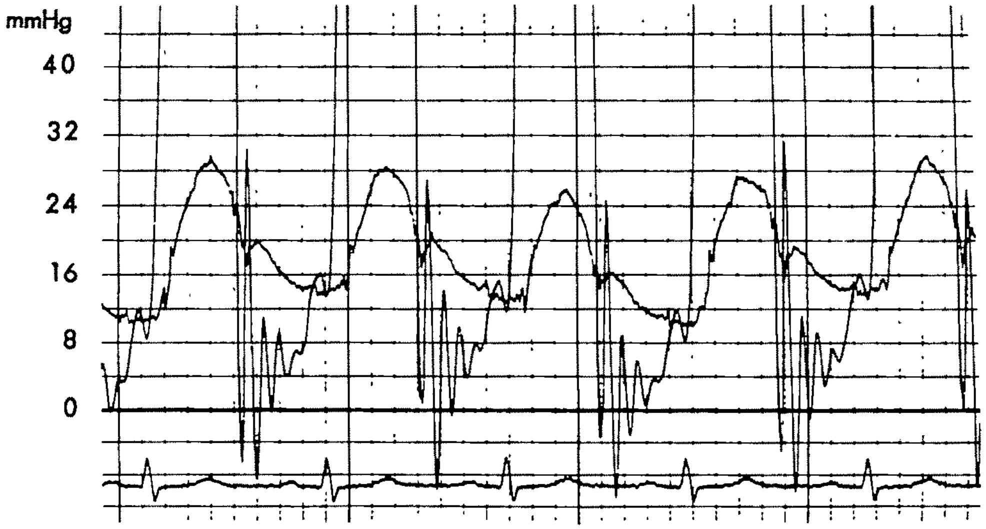

Fig. 5 *Left ventricular end diastolic pressure recorded by a fluid filled catheter and pulmonary artery pressure by transducer tipped catheter. Recordings were obtained in the catheter laboratory (paper speed 50 mm/s).*

CATHETER SPECIFICATION

The temperature coefficient of sensitivity was 0·2% per degree centigrade and the temperature coefficient of zero stability was 0·03%/full scale/degree centigrade. The sensitivity of the catheter was 5 μV/V/mm Hg and linearity was ±0·25% full scale. A zero drift of <1%/full scale/24 h was achieved after improvements to the elastomer covering the transducer.

CLINICAL EVALUATION

A total of 288 hours of ambulatory pulmonary artery pressure and electrocardiographic recording was obtained in 13 patients with two catheters. The minimum pulmonary artery diastolic pressure was 2 mm Hg and the maximum systolic pressure was 80 mm Hg. Simultaneous measurements of fluid filled and transducer tipped pulmonary artery presure as well as fluid filled ventricular end diastolic pressure were recorded in eight patients. Fluid filled pulmonary artery systolic pressure (mean (SD) 25·9 (7·9) mm Hg) was similar to transducer tipped systolic pressure (mean (SD) 27·8 (11·2) mm Hg). Fluid filled pulmonary artery diastolic pressure (mean (SD) 10·0 (4·8) mm Hg) was similar to transducer tipped diastolic pressure (mean (SD) 11·2 (4·6) mm Hg) and post "a" left ventricular end diastolic pressure (mean (SD) 10·9 (4·8) mm Hg). Transducer tipped

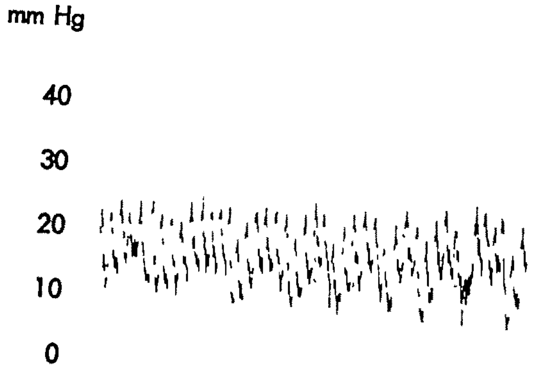

Fig. 6 *Compressed pulmonary artery trace obtained to show the effects of respiration on the recording. Inspiration reduces and expiration increases the pulmonary artery pressure. This reflects changes in the pleural space.*

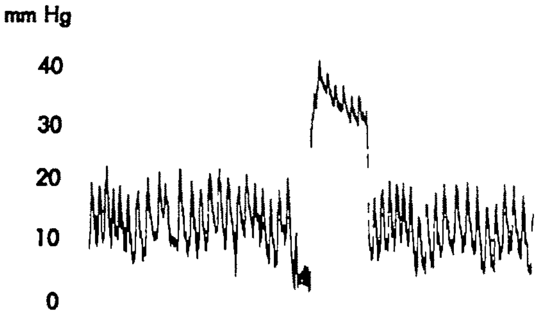

Fig. 7 *The effects of a Valsalva manoeuvre on transducer tipped pulmonary artery pressure.*

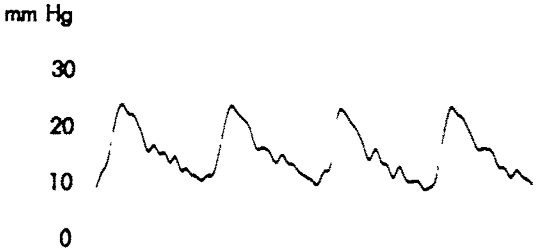

Fig. 8 *The recorded pulmonary artery pressure waveform played on to the optical writer*

pulmonary artery diastolic pressure correlated well ($r=+0{\cdot}99$, $p<0{\cdot}001$) with left ventricular end diastolic pressure (Fig. 5).

Figure 6 shows the effect of respiration and Fig. 7 the effect of the Valsalva manoeuvre on pulmonary artery pressure.

The pulmonary artery waveform played via the optical writer (Fig. 8) shows good preservation of the waveform when compared with Fig. 4. All recordings were obtained without the additional use of filters. During exercise in a 33 year old man with three vessel coronary artery disease there was a substantial rise in both the systolic and diastolic pulmonary artery pressures (Fig. 9).

## Discussion

Pulmonary haemodynamics in man were first studied by Cournand and Ranges who modified Forssmann's original techniques of venous catheterisation.[11,12] Recordings were limited to only a few minutes. Prolonged bedside monitoring was possible after catheter modifications,[13-15] but the equipment was not portable.[1,4,5] Problems with the zero reference point when fluid filled catheters are used have been overcome to some extent by placing the transducer at the level of the catheter tip.[7] For ambulatory use fluid filled catheters require a transducer-perfusion unit connected to tubing and anticoagulation with heparin. A change in posture from lying to standing altered the zero reference point for fluid filled catheters by about 4 mm.[6,16] Substandard recordings (20%) were due to repeated clotting of the catheter tip and damping of the pressure wave, kinking of the catheter or extension tubing, or both. Fluid filled catheters require a relatively bulky perfusion unit and are liable to artefacts such as overshoot, overdamping, and catheter whip.[8] They respond satisfactorily to a pressure which remains stationary but have limitations in fidelity when they are used to record varying pressure.

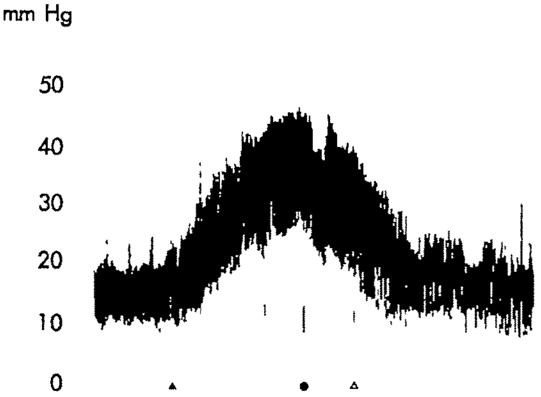

Fig. 9 *The effects of exercise on pulmonary artery pressure recorded from a 33 year old man with three vessel coronary artery disease. During exercise there was a rise in the pulmonary artery systolic and diastolic pressures which returned to basal levels when exercise stopped.* ▲, *start of exercise,* △, *end of exercise (8 minutes);* ●, *patient pressed event marker for chest pain.*

We have analysed the frequency and phase response of the transducer tipped system and have compared the results with a directly recorded fluid filled catheter. For the complete transducer amplifier-record-playback system, the amplitude response was flat to 8 Hz (−3 dB down). We have preserved the phase of the recorded signal and have shown that the phase response is linear to 8 Hz. Phase delay at 8 Hz exceeds the phase delay at 1 Hz by <30 ms. We have found no appreciable phase distortion up to 8 Hz.

Amplitude response will be constant over a selected band of signal frequencies (the passband) and will fall off at frequencies above and below the passband. The effects of this drop in amplitude response at low frequencies will be to increase artificially baseline stability at the expense of faithful reproduction of low frequency components (for example the diastolic period of a pressure waveform). For most pressure measuring systems, including that used in the present study, the low frequency response is adequate for faithful signal reproduction. At high frequencies, however, the drop in amplitude response (gain) of the system selectively attenuates the high frequency components of the waveform. If the high frequency response is severely limited then the greatest effect on the waveform will be on its fastest moving components—that is the upstroke—and thus the systolic pressure may be underestimated. The diastolic pressure is less likely to be affected by high frequency attenuation. As the heart rate increases from 70 to 150 beats per minute there is a slight decrease in harmonic power (20%) below 8 Hz. We have found that at 70 beats per minute 90% power is expressed below 8 Hz and this accords with other studies.[17] The loss of harmonic power with increasing heart rate is associated with some waveform distortion, but this tends not to affect diastolic pressure. The fluid filled system attenuates the amplitude of the frequency content (Fig. 3) including the first harmonic. This low frequency attenuation is greatly improved with a transducer tipped catheter with little loss in the Oxford recording.

Nathan *et al* first described continuous ambulatory pulmonary artery pressure monitoring with a transducer-tipped catheter.[7] The recording system was complex and expensive because it used a solid state system and computer analysis. The pulmonary artery pressure was averaged over 30 s, not beat to beat. The catheter required immersion in saline for five hours in order to minimise zero drift. We found that with improved elastomers this time could be reduced to one hour.

We have confirmed that in the absence of pulmonary vascular disease and mitral stenosis measurement by transducer tipped catheter of pulmonary artery end diastolic pressure correlates closely with left ventricular end diastolic pressure (Fig. 3).[1-3] If they are not handled carefully the transducer membranes are susceptible to damage that results in zero drift.

Most complications reported with long term pulmonary artery catheterisation with Swan-Ganz catheters have been due to impaction of an inflated balloon in a distal branch of the pulmonary artery.[18 19] In two patients in our study the transducer tipped catheter tip changed position and became slightly wedged. In one case this occurred after 18 h and in the other after 24 h. This had no apparent deleterious effects.

We have described a system of continuous pulmonary artery pressure recording in which every beat during periods of interest can be recorded and replayed. Thus most of the drawbacks of fluid filled catheters and the limitations of solid state transducer tipped systems have been overcome. This method could be used in any centre equipped for ambulatory electrocardiographic monitoring. The technique may be used to study the pathophysiology and treatment of coronary artery disease and cardiac failure as well as primary and secondary pulmonary hypertension.

We thank the Clinical Research Committee of the National Heart and Chest Hospitals for financial support.

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*Br Heart J* 1986; 55: 344–7

# Ultrafiltration in the management of refractory congestive heart failure

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SUMMARY Ultrafiltration was performed in nine patients with congestive cardiac failure that was refractory to conventional medical treatment. A mean of 12·7 litres of fluid was removed, and there was a sustained symptomatic improvement in all patients. Weight loss continued after ultrafiltration and a sustained increase in serum sodium concentration was also noted. A transient fall in right atrial pressure was seen only at four hours after ultrafiltration. No adverse haemodynamic effects were seen four and eighteen hours after fluid removal. Intracardiac dimensions measured by echocardiography remained unchanged. Ultrafiltration can be used to relieve symptoms in patients with refractory congestive heart failure and gross oedema.

Some patients with severe heart failure and gross peripheral oedema are resistant to conventional forms of medical treatment including vasodilators. In addition some patients become unresponsive to treatment because of the development of pharmacological tolerance or because of a further deterioration in cardiac function. Management of patients with refractory congestive heart failure is difficult because they have a poor prognosis and distressing symptoms of dyspnoea and gross peripheral oedema. The removal of large volumes of extracellular fluid by venesection, haemodialysis, and peritoneal dialysis is likely to provide such patients with symptomatic relief[1] but is limited by the tendency for adverse haemodynamic effects, such as hypotension and tachycardia, to develop.

Ultrafiltration, however, is a rapid method of selectively removing body water in which controlled fluid removal can prevent sustained haemodynamic upset.[2 3] In addition ultrafiltration can be performed by a venous technique and is less likely than haemodialysis to cause adverse haemodynamic effects.[4 5] Though symptomatic improvement has been demonstrated after ultrafiltration in individual patients with refractory congestive heart failure,[6-8] there are no data on its haemodynamic effects. The aim of this study was to assess the symptomatic and haemodynamic response to ultrafiltration of patients who had severe congestive heart failure that was resistant to conventional forms of medical treatment.

## Patients and methods

All patients admitted with chronic congestive heart failure over a three year period were considered for ultrafiltration. In order to maintain an haemodynamically stable study population patients with valvar heart disease were excluded. Only nine patients remained in congestive heart failure with gross peripheral oedema after they had been treated with diuretics, vasodilators, and inotropic agents. These were the patients in whom we tried ultrafiltration (Table). Their ages ranged from 47 years to 65 years (mean 53 years). Fluid intake was restricted to 1 litre per day. The mean dose of frusemide was 600 mg/day (range 160–1000 mg/day) either orally or by intravenous infusion. Vasodilator treatment was continued in six patients. All patients had New York Heart Association class IV symptoms and all had gross peripheral oedema. Informed consent was obtained from all patients.

The following were measured daily—weight (kg); fluid balance; heart rate; systemic blood pressure (standard cuff sphygmomanometry); and serum

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Accepted for publication 10 December 1985

Table *Data on nine patients with congestive heart failure who were treated by ultrafiltration*

| *Patient* | *Sex* | *Age* | *Aetiology* | *Daily drug treatment* |
|---|---|---|---|---|
| 1 | M | 49 | Coronary artery disease | Frusemide 1000 mg, spironolactone 100 mg, digoxin 0 25 mg |
| 2 | M | 47 | Congestive cardiomyopathy | Frusemide 160 mg, spironolactone 100 mg, captopril 75 mg |
| 3 | M | 51 | Restrictive cardiomyopathy | Frusemide 500 mg, spironolactone 100 mg, isosorbide dinitrate 40 mg, nifedipine 40 mg |
| 4 | M | 49 | Coronary artery disease | Frusemide 240 mg, spironolactone 100 mg, digoxin 0 125 mg, captopril 75 mg |
| 5 | F | 65 | Congestive cardiomyopathy | Frusemide 1000 mg, spironolactone 200 mg, prazosin 4 mg |
| 6 | M | 49 | Restrictive cardiomyopathy | Frusemide 250 mg, spironolactone 100 mg, digoxin 0 25 mg, captopril 37 5 mg |
| 7 | M | 56 | Coronary artery disease | Frusemide 1000 mg, spironolactone 200 mg, digoxin 0 25 mg, |
| 8 | M | 59 | Congestive cardiomyopathy | Frusemide 320 mg, spironolactone 200 mg, digoxin 0 125 mg, prazosin 9 mg |
| 9 | F | 47 | Congestive cardiomyopathy | Frusemide 1000 mg, spironolactone 200 mg |

urea, creatinine, and electrolytes. In six patients invasive haemodynamic monitoring and simultaneous M mode echocardiography were performed before and four hours and eighteen hours after the completion of each ultrafiltration procedure.

### HAEMODYNAMICS

A Swan-Ganz catheter was inserted by internal jugular venous cannulation and manipulated into the right main pulmonary artery. The right atrial, pulmonary artery, and pulmonary capillary wedge pressures were measured and cardiac output was evaluated by the thermodilution technique by means of an IL 720 cardiac output computer. All measurements were made in triplicate and the mean of these results was taken.

### ECHOCARDIOGRAPHY

M mode echocardiograms were obtained with an SKI Ekoline echocardiograph and left atrial, right ventricular, left ventricular end diastolic, and left ventricular end systolic dimensions were measured.

### ULTRAFILTRATION

Ultrafiltration was performed by venous cannulation through a double lumen dialysis cannula in two patients, via the femoral approach in eight patients, and by the internal jugular approach in one. In seven patients a Gambro AK10 machine was used with a Cordis-Dow 1·5 m$^2$ cellulosic based membrane. In two patients a Fresenius A2008C machine was used with a new highly permeable polysulphone membrane (F60). The latter has the advantage of providing improved permeability and biocompatability.[9 10] Ultrafiltration was continued until the development of either distressing muscle cramps or sustained hypotension. If peripheral oedema persisted the procedure was repeated on subsequent days depending on patient tolerance.

### STATISTICAL METHODS

We used the paired Wilcoxon test for statistical analysis.

## Results

The overall fluid loss ranged from 3·7 litres to 23 litres (mean 12·7). Ultrafiltration was performed 2–5 times per patient (mean 2 9) and lasted 45 minutes to 12 hours (mean 3·8 hours). The amount of fluid removed at each procedure was 1·7–6·0 litres (mean 3·0 litres) with the standard cellulosic membrane and 20 and 23 litres on the two occasions on which the polysulphone membrane was used. Each individual treatment was stopped because of muscle cramps or sustained hypotension. Transient

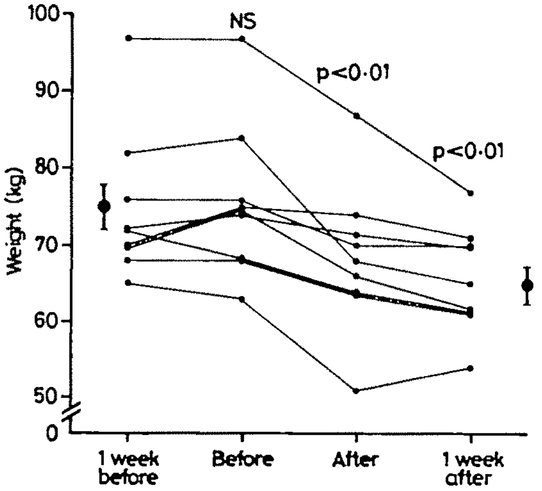

Fig. 1 *Weights (kg) of individual patients and mean (SEM) measured one week before ultrafiltration, after the completion of ultrafiltration, and at one week after fluid removal.*

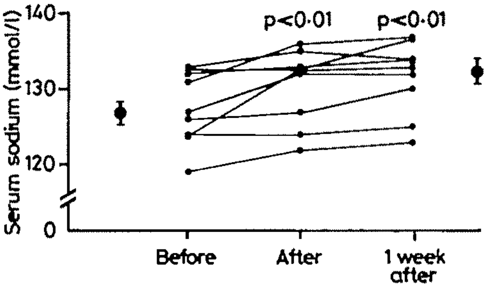

Fig. 2 *Serum sodium concentrations for individual patients and mean (SEM) shown immediately before, after the completion of ultrafiltration, and at one week after ultrafiltration.*

hypotension developed in all patients during the procedure; this responded rapidly to temporary discontinuation of fluid removal or, in four patients, to intravenous infusion of 20 g of albumin. Ultrafiltration was discontinued when it was considered clinically that the maximum benefit had been obtained.

Figure 1 shows patients' weights over the study period. No significant change in weight was seen during the week before ultrafiltration, indicating both a stable clinical state and a lack of response to drug treatment. Significant weight reduction occurred after ultrafiltration and continued in the week after the completion of ultrafiltration, indicating an improved response to diuretic treatment. Figure 2 shows the serum sodium concentrations. There was a significant increase in the serum sodium concentration after ultrafiltration and this increase was sustained over the subsequent week. No significant change occurred in either the serum urea or creatinine concentrations over the study period. Mean (SD) albumin concentration was unchanged (33 (4) g/l *vs* 35 (5) g/l) after ultrafiltration, despite the infusion of intravenous albumin during the procedure in four patients.

### HAEMODYNAMICS

Right atrial pressure was significantly reduced four hours after the completion of ultrafiltration, though by 18 hours it had returned towards the value before ultrafiltration. No change was seen in the heart rate, mean systemic blood pressure, or mean pulmonary artery pressure. Pulmonary capillary wedge pressure (mean (SD)) which was 26 (6) mm Hg before ultrafiltration was unchanged four hours (27 (6) mm Hg) and 18 hours (31 (9) mm Hg) after completion of each ultrafiltration period. Similarly cardiac output (mean (SD)) which was 3·2 (0·7) l/min before ultrafiltration remained unchanged four hours (3·3 (0·6) l/min) and 18 hours (3·3 (0·4) l/min) after each procedure. Echocardiographic measurement of intracardiac dimensions remained unchanged throughout.

### PROGRESS AFTER ULTRAFILTRATION

Symptoms improved and all patients became considerably less distressed immediately after ultrafiltration. Two patients who were non-insulin dependent diabetics developed systemic infection after ultrafiltration; the one with cellulitis had been treated for staphylococcal septicaemia before ultrafiltration. The source of infection in both cases was related to the indwelling Swan-Ganz catheter used for haemodynamic monitoring and not to the ultrafiltration procedure itself. In both cases staphylococci were isolated from blood culture within one week of ultrafiltration. Antibiotic treatment was successful in one, but the other patient died of ventricular fibrillation five days after the start of antibiotic treatment. Two patients were readmitted within three months of ultrafiltration with recurrence of peripheral oedema. Both these patients responded quickly to increased diuretic treatment and were able to be discharged home free of oedema after a short hospital admission. The remaining patients were free of oedema during subsequent follow up and one patient improved to New York Heart Association class III.

There were two hospital deaths after ultrafiltration. One patient with congestive cardiomyopathy and staphylococcal septicaemia died of documented ventricular fibrillation and the other, a patient with restrictive cardiomyopathy, of progressive deterioration in heart failure. A further five patients died during subsequent follow up (mean time to death 3·4 months, range 1–9 months). Sudden cardiac death was the presumed cause of all deaths and all the patients had remained free of oedema since ultrafiltration. The two surviving patients were oedema free throughout the subsequent year of follow up.

## Discussion

This study has demonstrated that ultrafiltration is a safe, effective, and relatively simple method for producing symptomatic improvement in patients with refractory congestive heart failure.

The ultrafiltration procedure used in this study has several advantages in the management of these patients. First, the rate at which fluid is removed can be accurately controlled by altering the transmembrane hydrostatic pressure. This fine control of fluid removal is of considerable importance in preventing sustained haemodynamic upset in patients who are already haemodynamically compromised. Towards the end of the study a new highly permeable, biocompatible filter became available and was used in two patients. In both of them over 20 litres of fluid was removed during a single ultrafiltration procedure. Use of this type of membrane may make it possible to render patients oedema free without the need for repeated intervention. The other major advantage is that vascular access is simple and necessitates only percutaneous central venous cannulation.

In our patients there was a significant improvement in serum sodium concentration, which was of similar magnitude to that found after ultrafiltration in fluid overloaded patients with renal failure.[11] All patients experienced transient hypotension when fluid was removed too rapidly during ultrafiltration. This was confirmed by pulmonary capillary wedge pressure measurement made in one patient during the procedure. When fluid was removed too rapidly from the intravascular compartment the wedge pressure fell from 30 mm Hg to 12 mm Hg with consequent fall in cardiac output and blood pressure. When ultrafiltration was transiently discontinued and intravenous albumin was infused, there was a rapid return to a stable haemodynamic state as the wedge pressure increased to 28 mm Hg. We therefore advise that the ultrafiltrate should be removed at a rate of less than 400 ml per hour and that intravenous albumin should be infused in hypoalbuminaemic patients in order to redistribute fluid from the interstitium into the intravascular compartment and promote removal by ultrafiltration.

As expected the reduction in weight found immediately after ultrafiltration reflected the amount of fluid removed during the procedure. Weight reduction continued over the week after ultrafiltration, however, and since fluid intake was restricted to one litre daily before and after ultrafiltration this indicates an improved response to diuretic treatment. This finding has been reported in fluid overloaded patients without pump failure[11] but its mechanism remains unclear. Though improved absorption of diuretic due to improvement of intestinal oedema may play a part in some patients, the continued weight reduction was also seen in those patients on intravenous therapy. In the absence of improved haemodynamics, an effect on the renin angiotensin system or a resetting or baroreceptors must be postulated as a possible underlying mechanism.

Though sustained symptomatic relief from gross oedema was achieved in these patients there was no improvement in haemodynamic variables, except for a transient fall in right atrial pressure. This finding is not surprising in patients in whom the underlying pathophysiological mechanism is primary myocardial failure, since ultrafiltration is dealing only with the secondary effects. Nor can it be expected to improve outcome in a group of patients with such a poor prognosis.

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# Heart rate variability in healthy subjects: effect of age and the derivation of normal ranges for tests of autonomic function

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SUMMARY The diagnosis of autonomic neuropathy frequently depends on results of tests which elicit reflex changes in heart rate. Few well-documented normal ranges are available for these tests. The present study was designed to investigate the effect of age upon heart rate variability at rest and in response to a single deep breath, the Valsalva manoeuvre, and standing. A computerised method of measurement of R-R interval variation was used to study heart rate responses in 310 healthy subjects aged 18–85 years.

Heart rate variation during each procedure showed a skewed distribution and a statistically significant negative correlation with age. Normal ranges (90% and 95% confidence limits) for subjects aged 20–75 years were calculated for heart rate difference (max − min) and ratio (max/min) and standard deviation (SD). Heart rate responses were less than the 95th centile in at least one of the four procedures in 39 (12·6%) out of the 310 subjects, and were below this limit in two or more tests in five (1·6%) subjects. In view of the decline in heart rate variation with increasing age, normal ranges for tests of autonomic function must be related to the age of the subject.

In recent years several simple, non-invasive tests of autonomic function have been described.[1 2] These tests are based on measurement of reflex changes in heart rate in response to standardised stimuli, such as the Valsalva manoeuvre,[3] single[4] or repeated deep breaths,[5] passive tilting, or standing.[6 7] More complex procedures, such as lower body negative pressure[8] and injection of pressor agents,[9] provide additional information about autonomic control of the cardiovascular system but are not suitable for routine clinical use.

Assessment of heart rate variability in subjects of all ages is, however, complicated by changes that occur in the autonomic nervous system with advancing age.[10] These changes include a gradual increase in basal and stimulated plasma noradrenaline concentrations,[11] altered adrenoceptor function,[12] and diminished responsiveness to adrenergic agonists and antagonists.[13] The heart rate response to the Valsalva manoeuvre and deep breathing tests declines with age in normal subjects.[3 14] Consequently normal ranges for such procedures that quote a single limit for all ages,[15] with or without a borderline range, are inappropriate and will result in errors in diagnosis, particularly in the elderly.

The present study was undertaken to evaluate the effect of age upon heart rate variation in a large group of healthy subjects, and thus to establish confidence limits for the heart rate response to standard tests of autonomic function.

## Subjects and methods

### SUBJECTS

A total of 310 healthy normal subjects, 147 males and 163 females, were studied. The age range was 18–85 years (mean (SD) 48 (17)); in each decade from 20 to 70 years of age there was a minimum of 50 subjects, approximately 50% males and 50% females (Table 1). Most of those aged less than 65 were factory employees, a few were hospital staff and healthy outpatients attending the physiotherapy department. Those aged 65–85 years were volun-

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Accepted for publication 17 December 1985

Table 1 *Age and sex distribution of subjects*

| *Sex* | *18–29 yr* | *30–39 yr* | *40–49 yr* | *50–59 yr* | *60–69 yr* | *70–85 yr* |
|---|---|---|---|---|---|---|
| M | 32 | 31 | 23 | 29 | 24 | 8 |
| F | 23 | 27 | 29 | 27 | 29 | 28 |
| Total (%) | 55 (17·7) | 58 (18·7) | 52 (16·8) | 56 (18·1) | 53 (17·1) | 36 (11·6) |

teers from day centres for the elderly in Bristol. Diabetic patients were excluded, as were those with cardiac failure, angina, cerebrovascular disease, and those taking drugs known to affect heart rate. None of the subjects had glycosuria.

### METHODS

Changes in heart rate were measured with an instantaneous cardiac ratemeter (Lectromed type 4522 model A) interfaced with a microcomputer (Commodore 4008N). Details of the method have been reported elsewhere.[10] The computer was programmed to record heart rate in either beats per minute or milliseconds per beat. A signal generated by an R wave simulator set at a rate of 60 $\text{min}^{-1}$ was measured with 100% accuracy over a period of two minutes.

Heart rate was measured continuously during four procedures in each subject as follows: (*a*) quiet supine rest for 60 s; (*b*) a single deep breath—the subject was asked to inhale deeply over 5 s and then to exhale over 5 s; (*c*) Valsalva manoeuvre—the subject was asked to maintain a pressure of 40 mm Hg for 15 s by means of forced expiration into a mouthpiece connected to a sphygmomanometer, the subject then lay quietly while heart rate was recorded for a further 45 s; (*d*) standing for 60 s (in this case the recording was started immediately the subject was erect). These are referred to hereafter as *resting, inspiration, Valsalva,* and *standing.* Subjects were supine or semirecumbent during (*a*)–(*c*). In addition blood pressure over the brachial artery was measured with a standard sphygmomanometer before and after the subject had stood for 60 s. All studies were performed by a single investigator (IAD O'B).

The following data were recorded from each test: maximum, minimum, mean, and SD of heart rate in beats/min. The values of the 15th and 30th beats after standing were noted also.[11] From these results, we derived the following indices of heart rate variation: heart rate difference (max − min), heart rate ratio (max/min), heart rate SD, and 30:15 ratio.

### STATISTICAL ANALYSIS

The influence of age and other variables on heart rate variation was examined by non-parametric techniques. Multiple correlation analysis was used to study the relation of age, resting heart rate, and blood pressure to heart rate variation. The difference in heart rate variability between males and females was compared by unpaired *t* tests. To derive confidence limits for indices of heart rate variation it was necessary to use a transformation technique because of the skewed distribution of results and the non-linear relation with age. Thus the original data were transformed to normality by the method of Box and Cox, in which a general power transformation is used to convert the original data to normality.[12] Confidence limits were then calculated and the data were transformed back.

Table 2 *The relative contribution of age, systolic blood pressure (BP), and basal heart rate to heart rate variation at rest and in response to the Valsalva manoeuvre, a single deep breath, and standing (values given are those of the change in $R^2$ at each stage in multiple correlation analysis)*

| *Index* | *Age* | *Systolic BP* | *Mean heart rate* |
|---|---|---|---|
| Heart rate difference: | | | |
| Resting | 23·0% | — | 0·2% |
| Inspiration | 32·6% | — | — |
| Valsalva | 20·5% | 0·8% | 4·0% |
| Standing | 33% | — | — |
| Heart rate ratio. | | | |
| Resting | 23·4% | — | 2·7% |
| Inspiration | 29·2% | — | 3·3% |
| Valsalva | 19·5% | 1·6% | — |
| Standing | 29·1% | — | 1·3% |
| Heart rate SD. | | | |
| Resting | 15·4% | — | — |
| Inspiration | 30·5% | — | — |
| Valsalva | 17·9% | 1·1% | 0·8% |
| Standing | 33·1% | — | — |

## Results

The correlation coefficient of heart rate indices with age ranged from −0·45 ($p<0·001$) for resting heart rate SD to −0·60 ($p<0·001$) for standing heart rate difference. Heart rate difference and SD were independent of resting heart rate in all tests, whereas heart rate ratio showed a weak correlation with resting heart rate in all procedures except for the Valsalva manoeuvre. There was also a significant negative correlation of heart rate variability with supine systolic blood pressure; however, this was due almost entirely to the dependence of blood pressure on age ($r=0·59$, $p<0·001$). Multiple correlation analysis showed that age accounted for 15–33% of variation in heart rate responsiveness in normal subjects, and that less than 4% was attributable to basal heart rate or blood pressure (Table 2).

Comparison of heart rate results between males and females was confined to subjects aged <70 years because of a preponderance of females above this age. Heart rate variability was generally less in women than in men; however, with the exception of heart rate ratio at rest ($p=0·004$), the difference did not reach statistical significance. Therefore, results from both sexes were analysed together.

The relative change in heart rate in response to the various procedures was Valsalva > standing > inspiration > resting. All indices of heart rate variability showed unimodal, positively skewed distributions. For example, Fig. 1 shows data for heart rate difference. Figure 2 shows the asymmetrical scatter of Valsalva ratios. It also illustrates the non-linear decline in heart rate responsiveness with increasing age and the 90% and 95% confidence limits derived by the transformation technique described above. The values of 90% and 95% confidence limits for heart rate difference, ratio, and SD in response to each procedure are given in Table 3.

Individual subjects rarely had results outside these limits in more than one test. Heart rate responses were less than the 95th centile in at least one of the four procedures in 39 (12·6%) out of 310 subjects. In the entire group heart rate difference results were outside the lower 95% confidence limit in two or more of the four tests in only two out of the 310 subjects (0·6%). Similarly, only three subjects (0·9%) had two or more abnormal heart rate ratios or SDs.

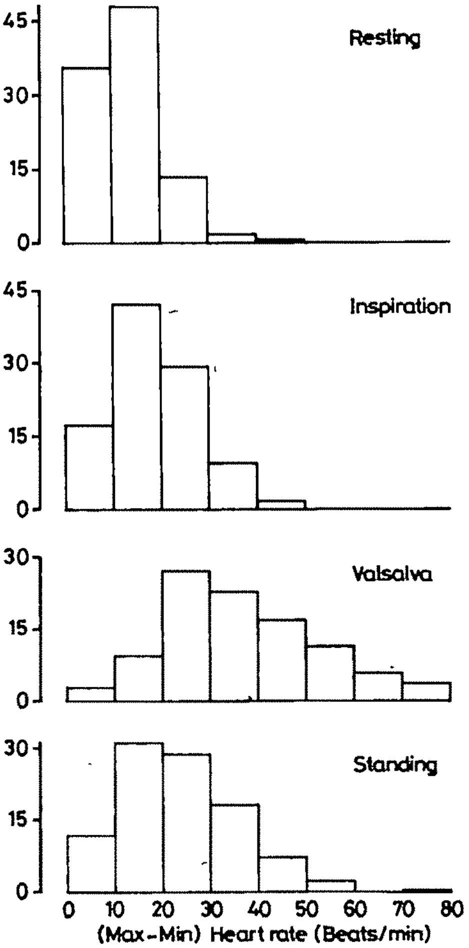

Fig. 1 *Heart rate differences in normal subjects measured at rest, during a single deep breath, Valsalva manoeuvre, and standing (n=310).*

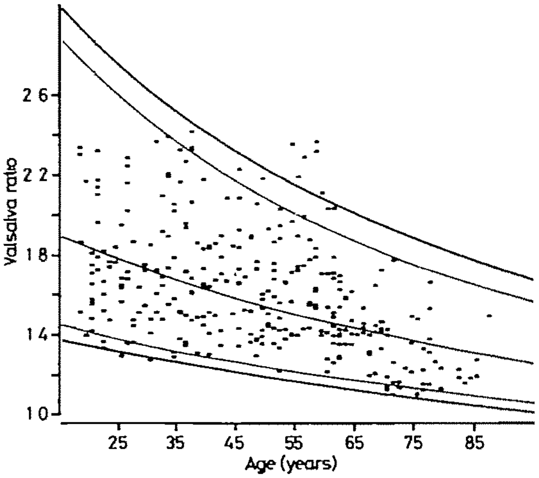

Fig. 2 *Age-related decline in the Valsalva ratio in normal subjects (n=310) and 90% and 95% confidence limits.*

Table 3 *Normal ranges for heart rate responses in normal subjects aged 20–75 years. Values given are (a) the lower 95% and (b) the lower 90% confidence limits*

| | *20 yr* | *25 yr* | *30 yr* | *35 yr* | *40 yr* | *45 yr* | *50 yr* | *55 yr* | *60 yr* | *65 yr* | *70 yr* | *75 yr* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Heart rate difference: | | | | | | | | | | | | |
| Resting | | | | | | | | | | | | |
| (a) | 7 | 7 | 6 | 6 | 5 | 5 | 5 | 4 | 4 | 4 | 3 | 3 |
| (b) | 9 | 8 | 7 | 7 | 6 | 6 | 5 | 5 | 5 | 4 | 4 | 4 |
| Inspiration | | | | | | | | | | | | |
| (a) | 11 | 10 | 9 | 8 | 7 | 6 | 5 | 5 | 4 | 3 | 3 | 2 |
| (b) | 13 | 12 | 11 | 10 | 9 | 8 | 7 | 6 | 5 | 4 | 4 | 3 |
| Valsalva | | | | | | | | | | | | |
| (a) | 22 | 20 | 19 | 17 | 16 | 15 | 13 | 12 | 11 | 19 | 9 | 8 |
| (b) | 25 | 23 | 22 | 20 | 19 | 17 | 16 | 15 | 13 | 12 | 11 | 10 |
| Standing | | | | | | | | | | | | |
| (a) | 15 | 13 | 12 | 11 | 9 | 8 | 7 | 6 | 5 | 5 | 4 | 3 |
| (b) | 17 | 16 | 14 | 13 | 11 | 10 | 9 | 8 | 7 | 6 | 5 | 4 |
| Heart rate ratio: | | | | | | | | | | | | |
| Resting | | | | | | | | | | | | |
| (a) | 1·12 | 1·11 | 1·10 | 1·09 | 1·08 | 1·07 | 1·06 | 1·05 | 1·04 | 1·04 | 1·03 | 1·02 |
| (b) | 1·14 | 1·12 | 1·11 | 1·10 | 1·09 | 1·08 | 1·07 | 1·07 | 1·06 | 1·05 | 1·04 | 1·03 |
| Inspiration | | | | | | | | | | | | |
| (a) | 1·17 | 1·15 | 1·13 | 1·12 | 1·10 | 1·08 | 1·07 | 1·06 | 1·04 | 1·03 | 1·02 | 1·00 |
| (b) | 1·20 | 1·18 | 1·16 | 1·14 | 1·13 | 1·11 | 1·09 | 1·08 | 1·06 | 1·05 | 1·04 | 1·02 |
| Valsalva | | | | | | | | | | | | |
| (a) | 1·35 | 1·32 | 1·30 | 1·27 | 1·24 | 1·24 | 1·20 | 1·17 | 1·15 | 1·13 | 1·11 | 1·09 |
| (b) | 1·41 | 1·38 | 1·35 | 1·32 | 1·29 | 1·27 | 1·24 | 1·22 | 1·19 | 1·17 | 1·15 | 1·13 |
| Standing | | | | | | | | | | | | |
| (a) | 1·20 | 1·17 | 1·15 | 1·13 | 1·12 | 1·10 | 1·08 | 1·06 | 1·05 | 1·03 | 1·02 | 1·01 |
| (b) | 1·23 | 1·21 | 1·19 | 1·16 | 1·14 | 1·13 | 1·11 | 1·09 | 1·07 | 1·06 | 1·04 | 1·03 |
| Heart rate SD: | | | | | | | | | | | | |
| Resting | | | | | | | | | | | | |
| (a) | 1·6 | 1·5 | 1·4 | 1·3 | 1·3 | 1·2 | 1·1 | 1·1 | 1·0 | 1·0 | 0·9 | 0·9 |
| (b) | 1·8 | 1·7 | 1·6 | 1·5 | 1·4 | 1·4 | 1·3 | 1·2 | 1·1 | 1·1 | 1·0 | 1·0 |
| Inspiration | | | | | | | | | | | | |
| (a) | 3·6 | 3·2 | 2·9 | 2·5 | 2·2 | 1·9 | 1·6 | 1·4 | 1·2 | 0·9 | 0·8 | 0·6 |
| (b) | 4·3 | 3·9 | 3·5 | 3·1 | 2·7 | 2·4 | 2·1 | 1·8 | 1·5 | 1·3 | 1·1 | 0·9 |
| Valsalva | | | | | | | | | | | | |
| (a) | 6·0 | 5·6 | 5·1 | 4·7 | 4·3 | 3·9 | 3·5 | 3·2 | 2·9 | 2·6 | 2·3 | 2·1 |
| (b) | 7·2 | 6·6 | 6·1 | 5·6 | 5·1 | 4·7 | 4·3 | 3·9 | 3·6 | 3·2 | 2·9 | 2·6 |
| Standing | | | | | | | | | | | | |
| (a) | 3·6 | 3·3 | 2·9 | 2·6 | 2·3 | 2·0 | 1·7 | 1·5 | 1·3 | 1·1 | 0·9 | 0·8 |
| (b) | 4·3 | 3·9 | 3·5 | 3·1 | 2·7 | 2·4 | 2·1 | 1·9 | 1·6 | 1·4 | 1·2 | 1·0 |

The timing of maximum and minimum heart rates on standing was determined in 219 subjects: maximum heart rate occurred within 10 s in 77%. In contrast, the timing of minimum rate showed a much wider scatter. The 30:15 ratio was compared with (max/min) heart rate ratio on standing in 294 subjects. There was a significant correlation between both measurements (r=0·45, p<0·001). The 30:15 ratio was <1·00 in 43%, however, and thus this derived index consistently underestimated the true max/min ratio.

As expected, supine systolic blood pressure was positively correlated with age (r=0·59, p<0·001). The difference between supine and standing systolic blood pressure was independent of age (r= −0·01, p NS). Four subjects, all of whom were aged 60–65 years, had a fall in systolic pressure on standing of 20–25 mm Hg.

The reproducibility of the heart rate response to each procedure was assessed in a separate study of six healthy male subjects aged 20–35 years, each of whom was studied on five separate occasions over three days. Heart rate ratios were found to have a lower coefficient of variation than heart rate differences or SDs (Table 4).

## Discussion

Variation in heart rate, whether at rest or in response to a stimulus, is mediated by the combined effects of cardiac vagal and sympathetic nerves acting upon the sinoatrial node. The aim of simple clinical tests, such as were used in the present study, in which the

Table 4 *Coefficients of variation (mean (range)) of heart rate measurements in six normal subjects*

| | *Heart rate* | | *SD* |
|---|---|---|---|
| | *Difference* | *Ratio* | |
| Resting | 29% (18–44%) | 7% (6–9%) | 25% (12–34%) |
| Inspiration | 16% (7–28%) | 6% (2–9%) | 21% (13–34%) |
| Valsalva | 17% (4–29%) | 9% (4–16%) | 21% (2–27%) |
| Standing | 26% (12–31%) | 9% (4–16%) | 24% (10–41%) |

chronotropic response to standardised manoeuvres is measured, is to investigate the integrity of these autonomic control mechanisms. Assessment of heart rate variability is, however, complicated by changes in the autonomic nervous system that occur with advancing age.[13] These functional changes include a gradual increase in basal and stimulated plasma noradrenaline concentrations,[14] altered adrenoceptor function,[15] and diminished responsiveness to adrenergic agonists and antagonists.[16] The results of the present study demonstrate that age is an important determinant of heart rate variability in normal subjects. Thus, unless allowance is made for the physiological effects of aging, diminished heart rate variability in older subjects may be attributed incorrectly to disease.

In this study of more than 300 healthy subjects, care was taken to ensure an even distribution of age and sex. It was necessary to use a transformation technique to analyse the data because the distribution of results was skewed, and the deline in heart rate responsiveness with age was non-linear. Alternative transformation methods were used by Smith and Wieling to derive normal ranges for heart rate variation at rest[17] and in response to deep breathing,[17 18] the Valsalva manoeuvre,[19] and standing.[18] We have obtained slightly lower limits, probably due to the larger number and more uniform age distribution of our subjects. Many previous studies of cardiovascular autonomic function tests, particularly those of diabetic autonomic neuropathy, have been of small groups of subjects or narrow age ranges or both.[11 20 21] In some instances recommended normal limits have not taken account of observed reductions in heart rate variability in older subjects[3 22 23]; in others normal ranges have been defined "arbitrarily".[24]

Sinus arrhythmia is enhanced during $\beta$ adrenergic blockade[25] and is abolished by atropine.[5] Thus, although the precise mechanisms responsible for sinus arrhythmia are not fully understood, the efferent pathway is via cardiac vagal fibres. Respiratory-induced changes in heart rate are reduced in the elderly.[4 17 18 26 27] This may be due to altered vagal activity, since the chronotropic response to atropine is also reduced in older subjects.[28] Bennett *et al*, in a comparative study of cardiac autonomic function tests, found that resting R-R interval SD correlated negatively with mean heart rate, and that R-R interval SD was not useful in detecting subjects with impaired heart rate responsiveness.[9] In the present study, heart rate variability during quiet and deep breathing was independent of mean heart rate, and it was possible to derive age-related limits for resting heart rate variation. In studying the response to deep breathing we used a single breath rather than repeated breaths, since the magnitude of the change in rate is often greater during the first breath and diminishes thereafter.[9] Ewing and Clarke have recommended a normal range of >15 beats/min for heart rate difference during deep breathing, with 11–14 as borderline and <11 as abnormal.[29] Our results indicate that these limits are not applicable to subjects of all ages; our results (Table 3) are, however, similar to the limits obtained by Mackay *et al* and Sundkvist *et al* in subjects aged <50 years.[22 30]

The Valsalva manoeuvre elicits a complex series of haemodynamic events that result in activation of sympathetic and parasympathetic neurones. It has been suggested that the cardiac response to Valsalva should be represented by the increase or decrease in rate relative to the initial heart rate.[31] Both these indices, however, correlate closely with the Valsalva ratio, and the latter has the advantage of being independent of basal heart rate. In a study of 200 normal subjects by Levin, the Valsalva ratio decreased with age and 96% had ratios >1·5.[3] The normal ranges that we have calculated for the Valsalva ratio are lower than 1·5 at all ages, and are generally higher than the limit of 1·10 set by Ewing and Clarke.[29] Our results are, however, similar to the range found by Dyrberg *et al* in subjects aged 30–48.[20]

The increase in heart rate on standing diminishes with age[26] (Table 3). The ratio of the R-R intervals of the 30th and 15th beats after standing, the 30:15 ratio, has been proposed as an index of the reflex heart rate response to standing.[11] The mechanisms underlying the immediate heart rate response to standing are complex,[7] and the present data indicate that these changes in rate are not accurately represented by the 30:15 ratio because of the high frequency of false positive results. Others have also found the 30:15 ratio to be unhelpful and to underestimate the true max/min ratio.[18 32]

Postural hypotension is a relatively common finding in the elderly. Caird *et al* found that 16% of 494 people aged more than 65 have a systolic fall >20 mm Hg on standing.[33] This degree of postural hypotension was less common among our subjects, occurring in only 4·5% of those aged 60 or more. This may have been due to differences in the study populations, since contributory factors were identified in 40% of Caird's subjects with postural hypotension and such individuals would have been excluded from the present study.

It is a contentious issue whether the response to tests of autonomic function should be expressed as the difference or the ratio of the induced change in heart rate (or R-R interval). Although the relation between these two indices is linear, the slope is dependent on basal heart rate (Fig. 3). Thus, if a

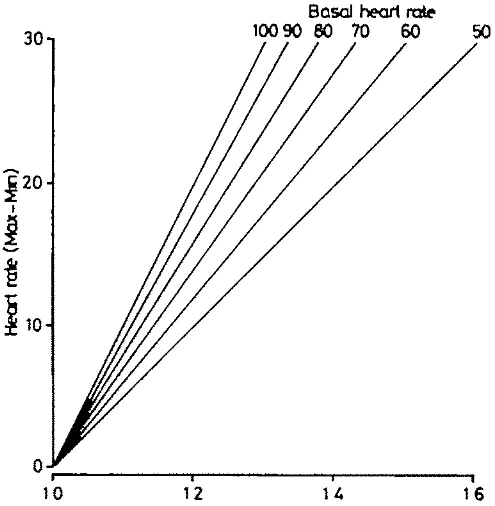

Fig. 3 *The effect of basal heart rate upon the relation between heart rate difference (max – min) and heart rate ratio (max/min).*

particular test induces a heart rate difference of 20 beats/min the corresponding heart rate ratio will be 1·33 for a basal heart rate of 60, 1·20 for a basal rate of 100, and 1·17 for a basal rate of 120. Furthermore, it is not known whether a change in heart rate from 60 to 80 is comparable physiologically to a change in rate from 100 to 120. Since there is no consensus on which index should be used to express the heart rate response, we have presented all our data after all three methods of analysis. The expression of heart rate data as either ratios or differences may also be relevant to the diagnosis of diabetic autonomic neuropathy. It is well documented that heart rates are, in general, faster in diabetics than in non-diabetics.[2 5 9 20] Consequently, autonomic dysfunction may be diagnosed more frequently if ratios rather than differences are used.

It is important to recognise that a diagnosis of autonomic neuropathy cannot be substantiated on the basis of the results from a single test.[29] Among the reasons for this are the variability of results in healthy subjects, the different physiological basis of the various tests, and, in the case of disease states, the patchy distribution of lesions within the autonomic nervous system. Using a combination of four simple procedures we have shown that <2% of a normal population will have more than one abnormal test result. We suggest, therefore, that abnormal autonomic control of heart rate can be diagnosed with confidence using these tests with age-related normal ranges.

We thank Dr R J Hunt, Department of Mathematics, Statistics and Operational Research, University of Exeter, for assistance and statistical advice.

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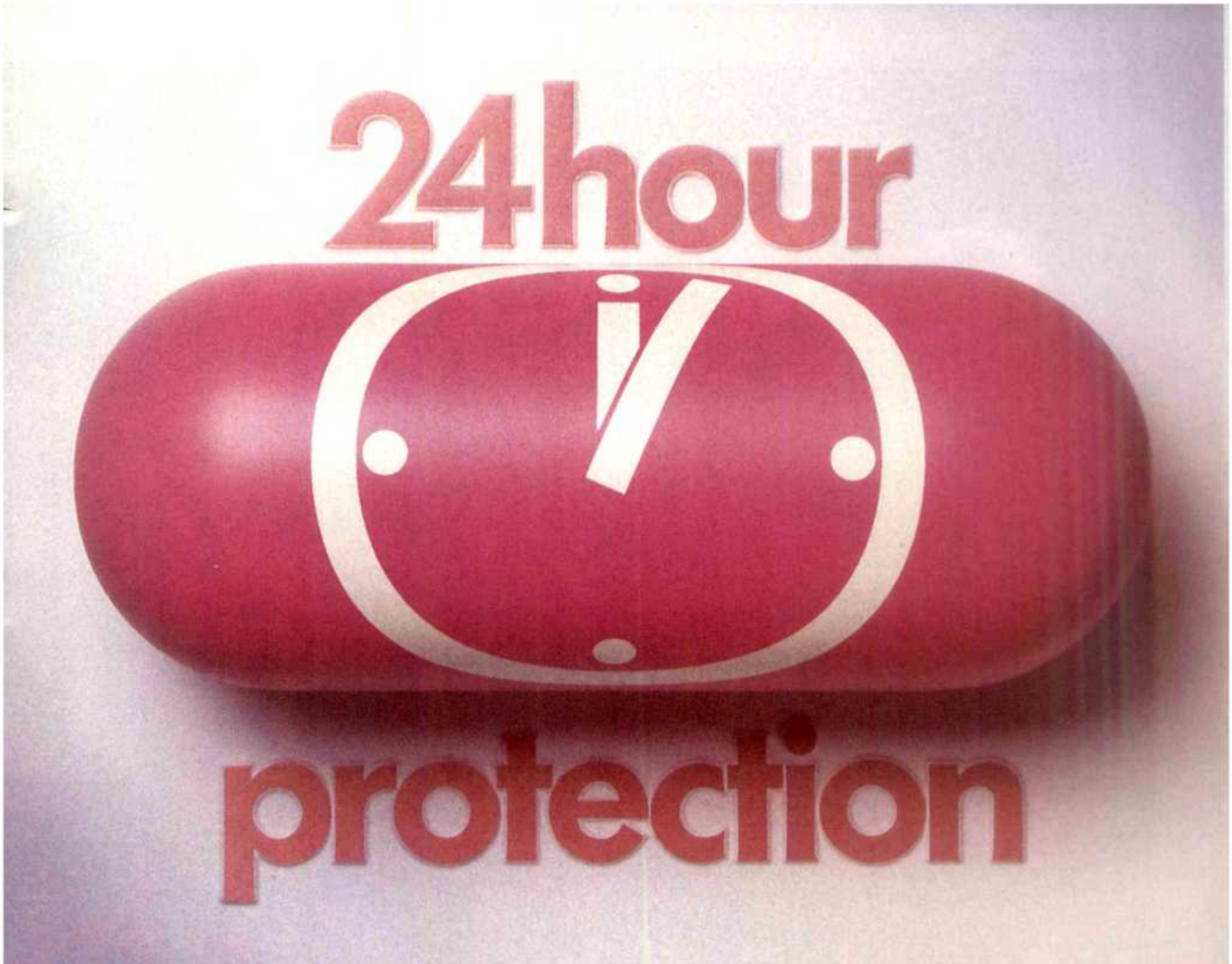

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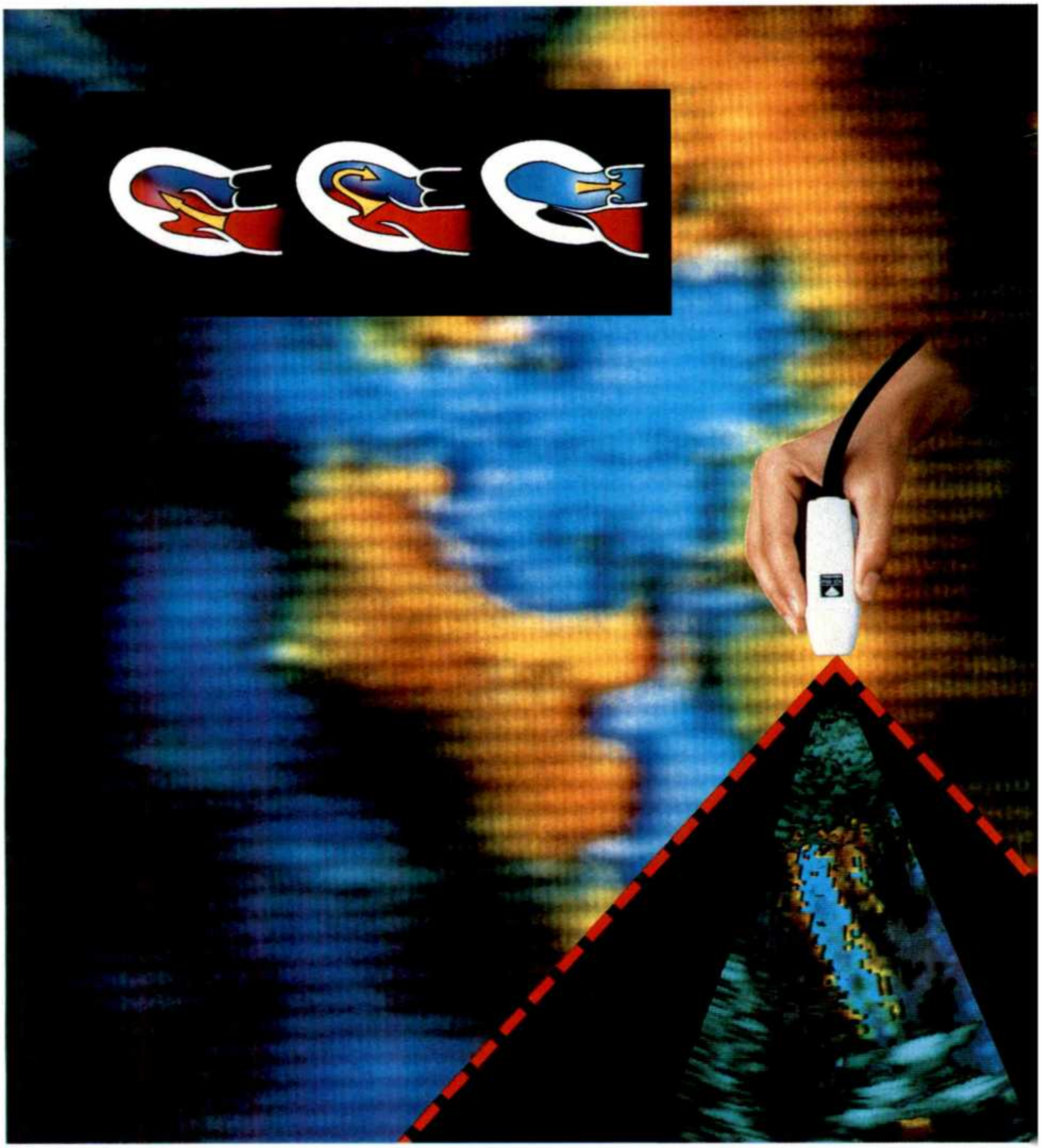

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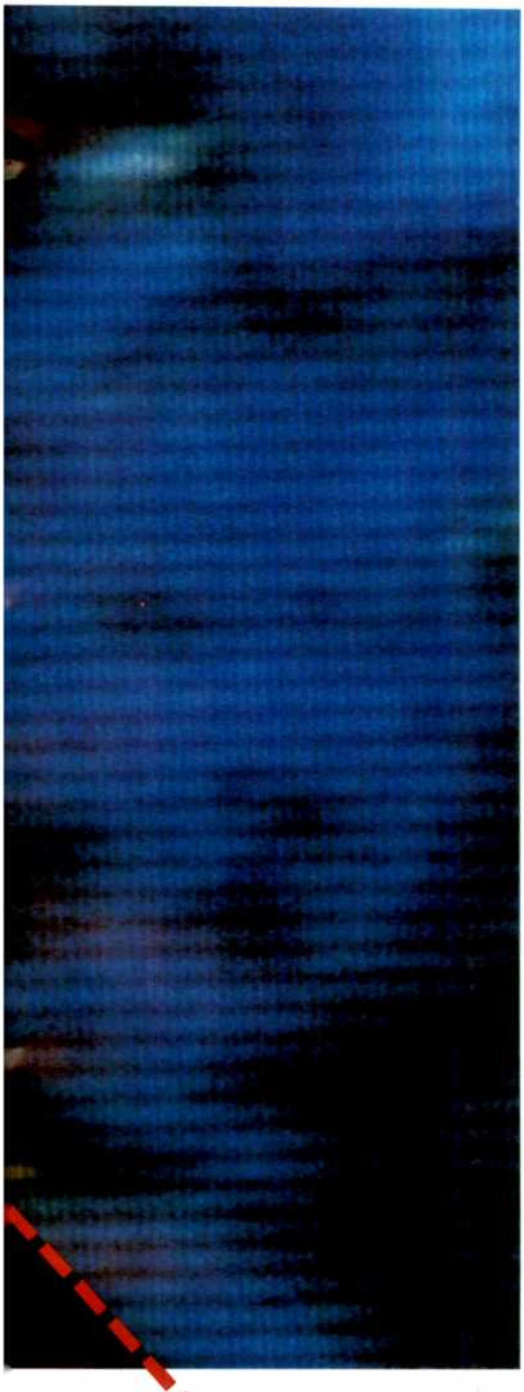

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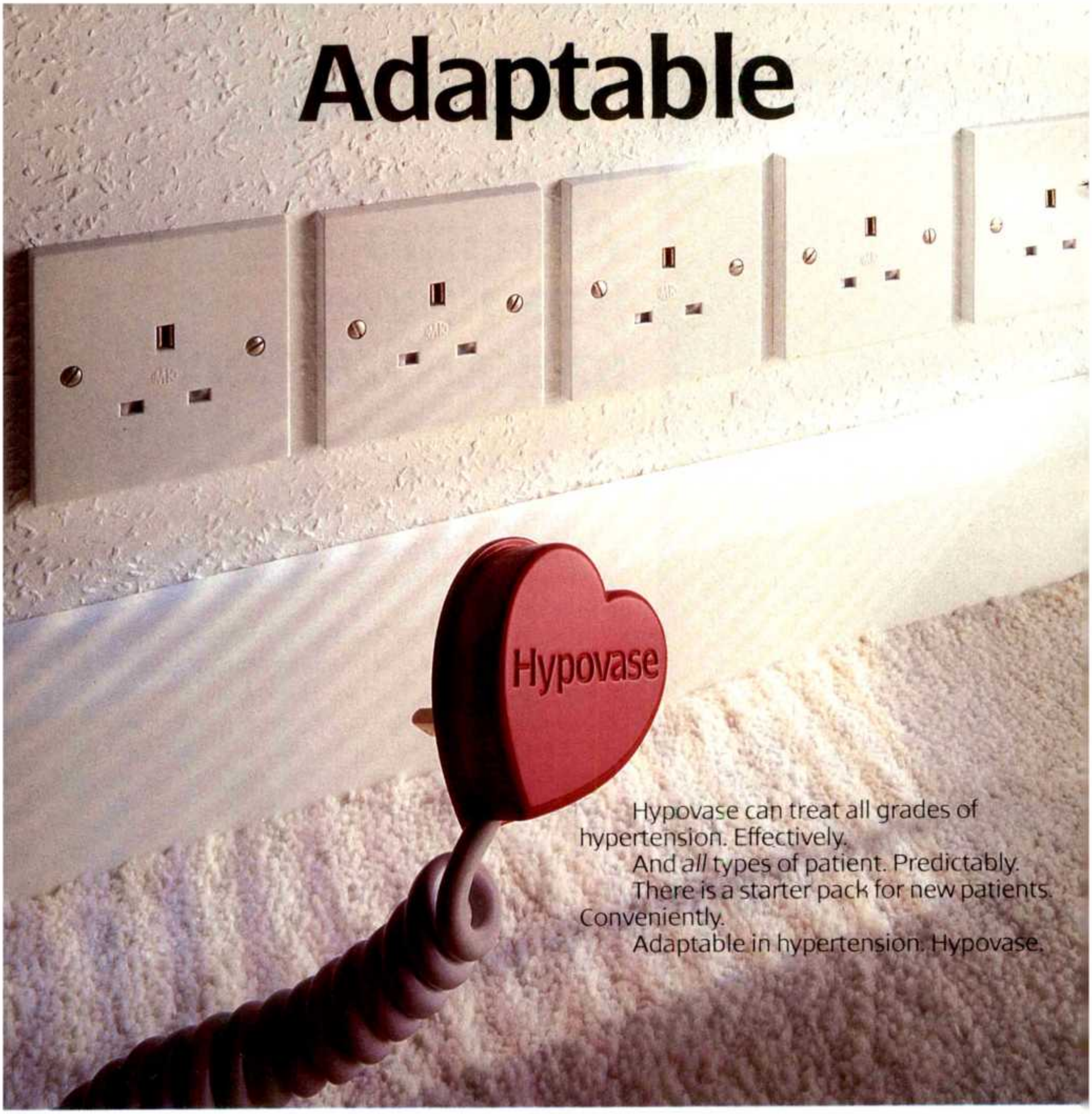

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# Mitral valve closure and left ventricular filling time in patients with VDD pacemakers

## *Assessment of the onset of left ventricular systole and the end of diastole*

HELENE VON BIBRA, ALEXANDER WIRTZFELD, ROGER HALL,* KURT ULM, HANS BLÖMER

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SUMMARY The effect of mitral valve closure on left ventricular filling time and its relation to the onset of systole were assessed from mitral valve echocardiograms and simultaneous apex cardiograms in 21 normal subjects, 11 patients with left bundle branch block, and 19 patients with VDD pacemakers programmed for atrioventricular intervals of 50, 150, and 250 ms. The interval between the electrocardiograph Q wave and the apex cardiogram upstroke was similar in normal subjects and patients with left bundle branch block, but was significantly longer in patients with VDD pacemakers at all atrioventricular intervals. Similarly there was little difference in the time interval between the Q wave and mitral valve closure in normal individuals and patients with left bundle branch block but this was considerably delayed in VDD pacemaker patients with the atrioventricular interval set at 50 ms. With increasing atrioventricular intervals the mitral valve closed significantly earlier, whereas the onset of left ventricular systole and the timing of mitral valve opening remained unchanged. Thus as a result of earlier mitral valve closure left ventricular filling time decreased progressively as the atrioventricular interval was increased. Since the onset of left ventricular systole, with respect to left ventricular stimulation, is considerably delayed in VDD pacemaker patients a short atrioventricular interval is required in these patients to maintain the normal time relations between atrial and ventricular contraction and hence maximise left ventricular filling.

Left ventricular filling provides the blood volume for subsequent left ventricular ejection. One of its important determinants is left ventricular filling time, which is determined by the mitral valve movement. This injection time depends not only on cardiac cycle length but also on the mechanisms which time mitral valve closure. The timing of mitral valve closure can be altered by electrical delay of ventricular depolarisation[1-3] and in atrioventricular conduction disturbances.[4-6] These two conditions coexist in patients with dual chamber pacemakers since ventricular depolarisation begins from an abnormal focus and is delayed and the PR interval can be altered by programming the pacemaker. Since the relative timing of atrial and ventricular contraction can be altered simply by reprogramming the pacemaker these patients offer a unique opportunity to study the effect of these events on mitral valve movements and left ventricular filling time.

This study was designed to examine non-invasively the relations between electrical and mechanical events in patients with VDD pacemakers over a wide range of atrioventricular intervals. The movements of the mitral valve and hence left ventricular filling time were detected by M mode echocardiography as was aortic valve opening which times the onset of left ventricular ejection. The onset of mechanical systole was detected by the upstroke

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Accepted for publication 17 December 1985

of an apex cardiogram and electrocardiogram. A group of normal controls was studied. Finally patients with left bundle branch block were also studied to examine the possible effects of conduction disturbance of a type similar to that seen in right ventricular pacing.

This information is of theoretical interest because of the insight that it gives into the mechanisms underlying mitral valve motion and particularly mitral valve closure. It is also of considerable practical importance. Patients with myocardial impairment who receive dual chamber pacemakers supposedly benefit from the improvement in left ventricular diastolic function produced by coordinating atrial and ventricular contraction. This study attempts to establish the atrioventricular intervals that provide the longest left ventricular filling time and thus should maximise the clinical benefits of this type of pacing.

## Patients and methods

We studied 51 patients who had been informed about the nature of the study and had consented to take part in it. These patients were divided into three groups:

*Control group*—There were 21 controls (12 men, 9 women; age range 24–57 years). Cardiac disease was excluded in these subjects by a normal history, physical examination, electrocardiogram, and chest *x* ray.

*Left bundle branch block*—There were 11 patients (seven men, four women; age range 39–70 years). They had normal PR intervals but left bundle branch block in association with the following diseases: hypertension (2), hypertrophic cardiomyopathy (3), congestive cardiomyopathy (3), ischaemic heart disease (1) and aortic valve replacement (2). This group was included so that we could investigate the effects of abnormal ventricular depolarisation of a type similar to that occurring in patients with right ventricular pacing.

*Pacemaker group*—There were 19 patients (11 men and eight women, age range 21–75 years) in this group. All showed the electrocardiographic pattern of left bundle branch block due to right ventricular stimulation by a dual chamber pacemaker. The pacemakers, all programmed in VDD mode, had been implanted for complete heart block (17 patients) or second degree heart block (2 patients) 3–18 months before the study. Ten of these patients had presented with symptoms of left ventricular failure (New York Heart Association grade II-III); three had ischaemic heart disease, and two had undergone aortic valve replacement. In the other nine patients without symptoms of left ventricular failure the aetiology of the heart block was not clear apart from one patient with congenital heart block and another with a history of myocarditis. All patients were studied with their VDD pacemakers programmed for the following atrioventricular intervals: 50, 150, and 250 ms. The protocol began with an atrioventricular interval of 150 ms, and this was followed by the two other intervals in random sequence. All measurements were made on beats in which ventricular pacing was triggered by a P wave after the programmed delay.

### INVESTIGATIONS

Echocardiograms to detect mitral and aortic valve movements were obtained from all patients by means of a Hewlett Packard 77020 A ultrasound system with a 3 5 MHz transducer. M mode echocardiograms were recorded both at the level of the aortic valve and the mitral valve at a paper speed of 100 mm/s. Electrocardiograms were recorded simultaneously in all patients. A simultaneous apex cardiogram was recorded in 10 randomly selected patients in each group. The apex cardiogram was recorded because the onset of its upstroke coincides with the onset of left ventricular pressure rise.[7] Thus mitral valve movements and electrocardiographic events could be related to the onset of mechanical systole in these subgroups. Each observation was the mean value of measurements taken from 10 consecutive cardiac cycles.

The following time intervals were measured from the preceding electrocardiographic pacemaker spike or Q wave as appropriate: (*a*) the onset of the upstroke of the apex cardiogram; (*b*) mitral valve closure (MC); (*c*) aortic valve opening (AO); (*d*) mitral valve opening (MO).

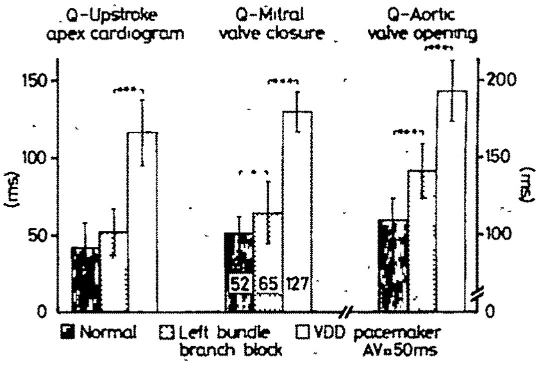

Fig. 1 *Timing (mean (SD)) of upstroke of apex cardiogram, of mitral valve closure, and of aortic valve opening with reference to the Q wave or the pacemaker spike in normal individuals, patients with left bundle branch block, and in patients with VDD pacemakers set at an atrioventricular interval of 50 ms.* $^{*}p<0\ 05$, $^{***}p<0\ 001$.

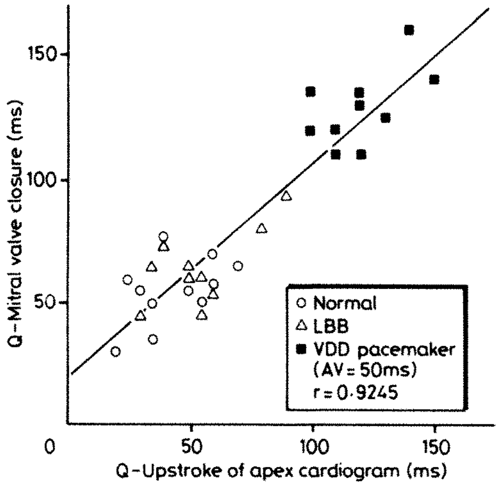

Fig. 2 *Correlation between onset of left ventricular systole (taken as timing of the apex cardiographic upstroke) and end of preceding diastole (taken as mitral valve closure) arranged in groups according to the increasing delay of intraventricular conduction—that is normal individuals, patients with left bundle branch block (LBB), and patients with VDD pacemakers set at an atrioventricular interval of 50 ms.*

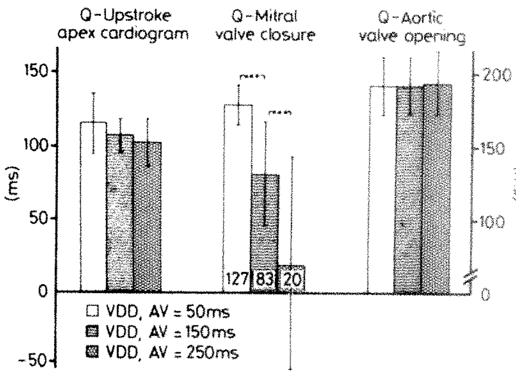

Fig. 3 *Timing (mean (SD)) of upstroke of apex cardiogram, of mitral valve closure, and of aortic valve opening in VDD pacemaker patients at atrioventricular intervals of 50, 150, and 250 ms.* ***$p < 0.001$.

The onset of mitral A wave (A) was timed from the *succeeding* pacemaker spike or Q wave and the cycle length (R-R interval) was also recorded.

LV filling time (FT, ms) was calculated as follows:

$$FT = RR - MO + MC$$

and normalised by expressing it as a percentage of cycle length (%FT).

$$\%FT = \frac{FT}{RR} \times 100$$

The statistical significance of differences between mean values in the three groups was analysed by the Kruskal Wallis test and by the Mann Witney test. Differences between mean values within the pacemaker group were analysed by the Friedman test and the Wilcoxon rank test. Correlation coefficients were calculated by the least squares method.

## Results

### *Increasing delay of intraventricular depolarisation, its influence on the end of diastole and onset of systole*

Figure 1 shows the intervals between the Q wave or pacing spike and the onset of the upstroke of the apex cardiogram, mitral valve closure, and aortic valve opening. In this section the results given were obtained with pacemakers programmed to an atrioventricular interval of 50 ms, from patients with left bundle branch block, and from normal controls. Mean cycle length was the same in all three groups of patients. The upstroke of the apex cardiogram occurred 44 (16) ms (mean (SD)) after the electrocardiographic Q wave in normal subjects and was similarly delayed (52 (18) ms) in patients with left bundle branch block. It was considerably delayed in pacemaker patients, occurring 119 (21) ms ($p < 0.001$) after the pacing spike. Mitral valve closure was 52 (11) ms after the Q wave in normal individuals and slightly later (65 (20) ms) in patients with bundle branch block ($p < 0.05$). It was markedly delayed in pacemaker patients being 127 (14) ms after the pacing spike ($p < 0.001$) compared with both other groups. Aortic valve opening demonstrated a similar pattern in the three groups. It occurred 111 (14) ms after the Q wave in normal subjects, 143 (19) ms after the Q wave in patients with left bundle branch block ($p < 0.001$), and 193 (20) ms after the pacing spike in pacemaker patients ($p < 0.001$).

A positive linear correlation was demonstrated between the onset of left ventricular systole (taken as the onset of the apex cardiographic upstroke) and the end of diastole (taken as mitral valve closure) (Fig. 2) in normal individuals, in patients with left bundle branch block, and in VDD pacemaker patients with an atrioventricular interval of 50 ms. The regression equation describing this relation for these patients with increasing delay of left ventricular depolarisation was $y = 0.9565x + 16$; $r = 0.93$.

### *Effects of increasing atrioventricular intervals on the end of diastole and onset of systole in paced patients*

Mitral valve closure occurred significantly earlier as the programmed atrioventricular interval was

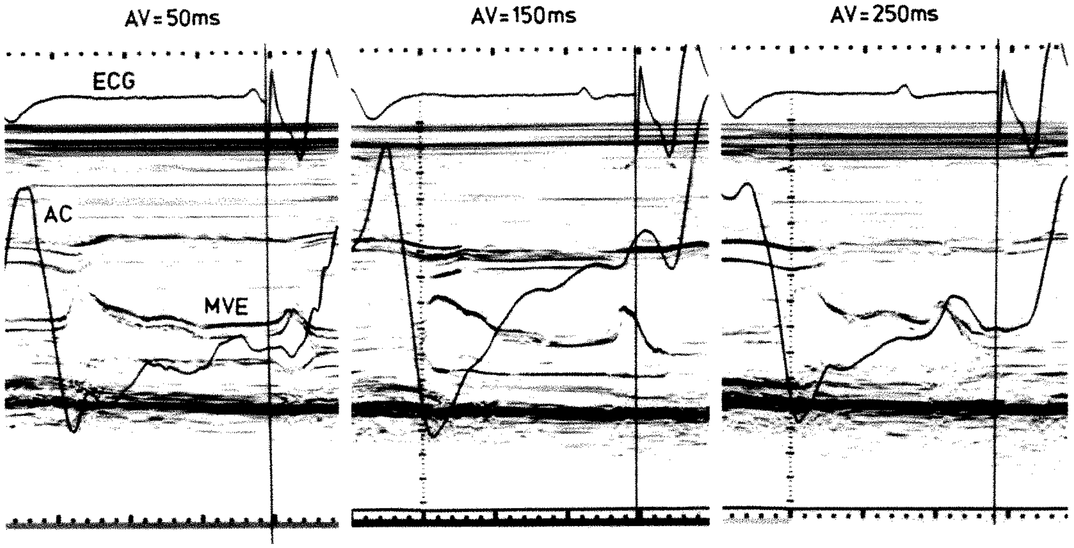

Fig. 4 *An M mode echocardiogram of the mitral valve and a simultaneous apex cardiogram during VDD stimulation with atrioventricular intervals of 50, 150, and 250 ms. Early mitral valve closure with respect to the pacemaker spike (marked by the vertical line) is present at an atrioventricular interval of 250 ms.*

increased (Fig. 3). This is shown in an original recording from a patient with a low heart rate (Fig. 4) and at a faster heart rate even more pronounced changes were found (Fig. 5). As the atrioventricular interval was increased so the scatter of the individual values increased. This is shown by the rising standard deviation in Fig. 3.

In contrast, alterations in the atrioventricular interval had no effect on the timing of the upstroke of the apex cardiogram (mechanical systole), aortic valve opening (the onset of left ventricular ejection) (Fig. 3), or mitral valve opening (the onset of diastole) (Fig. 6).

*Left ventricular filling time*

Figure 6 shows the sequence of timing of mitral valve movements in all three groups with reference to the Q waves or pacing spikes and also shows cycle

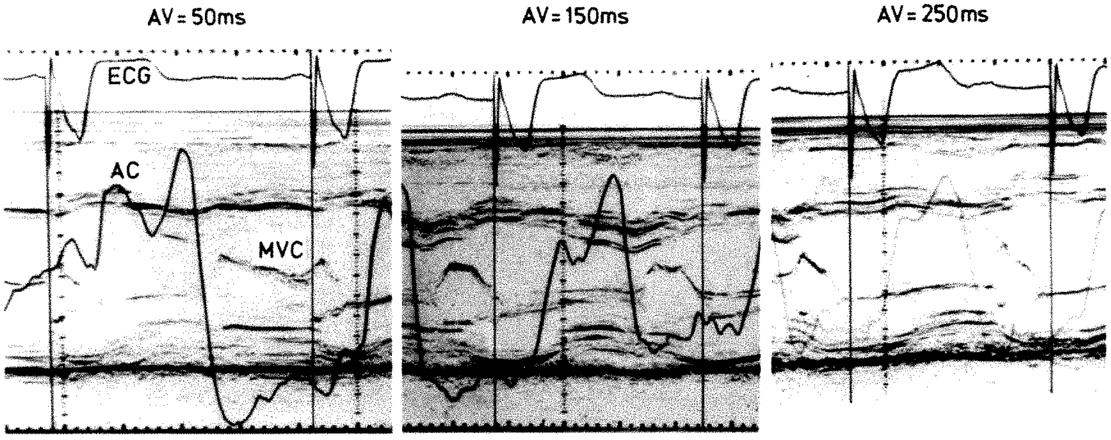

Fig. 5 *M mode mitral valve echocardiograms and apex cardiograms during VDD stimulation with atrioventricular intervals of 50, 150, and 250 ms in a patient with short cycle length. The mitral A wave is diminished at AV 150 ms and leaflets close early. The mitral A wave is not visible at AV 250 ms and leaflets close before the pacemaker spike, causing considerable reduction of left ventricular filling time.*

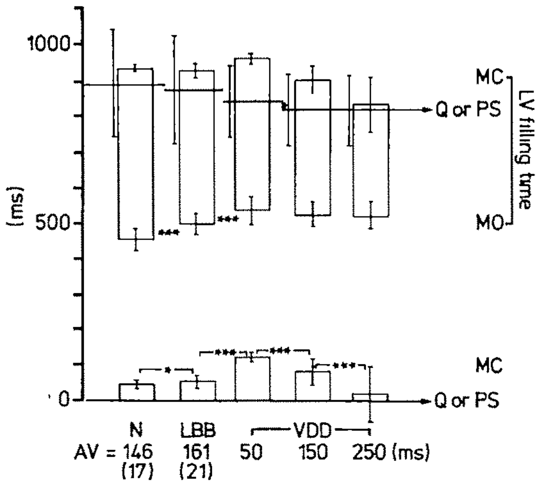

Fig. 6 *Timing (mean (SD)) of mitral valve movements (MC, closure; MO, opening) throughout the cardiac cycle (with the Q wave or pacemaker spike (PS) as reference points) in the group of normal individuals (N), in patients with left bundle branch block (LBB), and in patients with VDD pacemakers set at atrioventricular intervals of 50, 150, and 250 ms.*

length and the duration of left ventricular filling time. Mean cycle length was non-significantly different in controls, patients with left bundle branch block, and patients with pacemakers set with an atrioventricular interval of 50 ms. With increasing atrioventricular delay there was a small but significant decrease in cycle length (Fig. 6).

In the pacemaker patients left ventricular filling time significantly decreased with increasing atrioventricular intervals. It was 441 (94) ms at the atrioventricular interval of 50 ms, 372 (104) ms ($p<0\cdot03$) when the interval was 150 ms, and 304 (103) ms ($p<0\cdot02$ compared with a setting of 150 ms) when the interval was 250 ms. This reduction in left ventricular filling time was due to alterations in the timing of mitral valve closure since the timing of mitral valve opening was unchanged (Fig. 6).

Normalised left ventricular filling time was 53 (6)% in control subjects, somewhat less in patients with left bundle branch block (48 (7)%, $p<0\cdot025$), and did not differ from normal in pacemaker patients with an atrioventricular interval of 50 ms (50 (6)%). With increasing atrioventricular intervals there was a significant reduction to 45 (9)% ($p<0\cdot007$) when the atrioventricular delay was 150 ms, and to 38 (10)% ($p<0\cdot02$ compared with an interval of 150 ms) when the atrioventricular delay was 250 ms; both these values were significantly less than normal ($p<0\cdot004$ and $p<0\cdot001$).

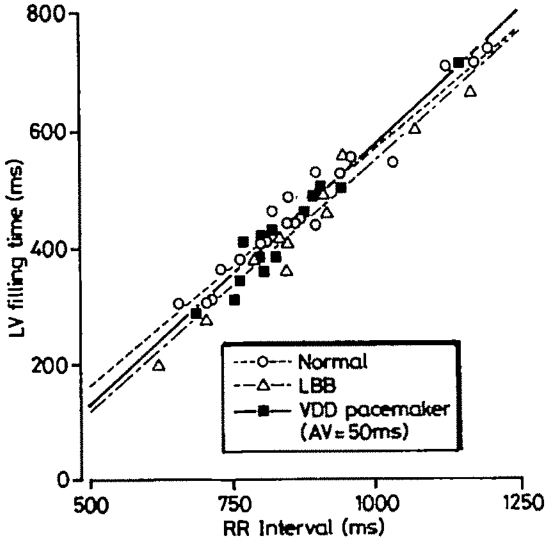

Fig. 7 *Correlation between left ventricular filling time and cycle length in the group of normal individuals, in patients with left bundle branch block (LBB), and in VDD pacemaker patients. The regression lines are given for each group.*

The well known correlation between filling time and cycle length is demonstrated in Fig. 7 for normal individuals ($r=0\cdot97$), patients with left bundle branch block ($r=0\cdot98$), and VDD pacemaker patients at an atrioventricular interval of 50 ms ($r=0\cdot93$). Clearly these regression lines are not different from each other. The equation for all indi-

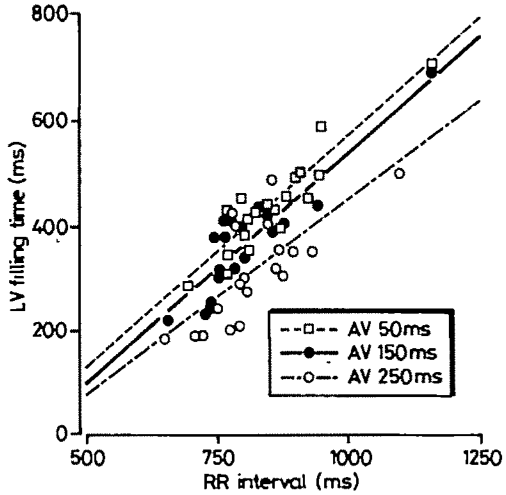

Fig. 8 *Correlation between left ventricular filling time and cycle length in 19 VDD pacemaker patients at atrioventricular intervals of 50, 150, and 250 ms.*

viduals was $y = 0{\cdot}857x - 292$ ($r = 0{\cdot}96$). With longer atrioventricular intervals, however (Fig. 8), the line was shifted downwards. The equations were $y = 0{\cdot}909x - 334$ for an atrioventricular delay of 50 ms, $y = 0{\cdot}892x - 350$ at a delay of 150 ms, and $y = 0{\cdot}767x - 311$ when the delay was 250 ms; the final value is significantly different from that seen with an interval of 50 ms ($p < 0{\cdot}001$).

### *Mitral A wave*

The onset of the mitral A wave, signifying the mechanical effect of atrial contraction, occurred 81 (23) ms before the next Q wave in normal controls, 86(28) ms before the next Q wave in patients with left bundle branch block, and only 5 (17) ms before the pacing spike in pacemaker patients in whom the atrioventricular interval was set at 50 ms ($p < 0{\cdot}001$ compared with both controls and left bundle branch block patients). As the atrioventricular interval was increased in the pacemaker patients the onset of the mitral A wave occurred, as expected, at increasingly longer intervals before the pacing spike. These intervals were 76 (24) ms ($p < 0{\cdot}01$) when the atrioventricular delay was 150 ms and 148 (38) ms ($p < 0{\cdot}001$) when the delay was 250 ms. As the mitral A wave occurred longer before the pacing spike it began to exert an effect on mitral closure not seen with shorter atrioventricular delays when mitral closure occurs as a result of ventricular systole. This resulted in the correlation between onset of left ventricular systole and mitral valve closure being lost when the atrioventricular delay was long.

## Discussion

Because of the short time available in the cardiac cycle and the large number of events occurring during it, considerable synchronisation between myocardial and valve movement is necessary if the heart is to function efficiently. The study of time intervals in the cardiac cycle has a long history.[8] It has mainly concentrated on systolic events, despite the fact that asynchrony during diastole is of great importance since any impairment in ventricular filling must result in an equivalent impairment or ejection.

In 1921 Wiggers defined the onset of systole as coinciding with the closure of the atrioventricular valves.[9] Subsequent use of phono- and echocardiography has shown many exceptions to this definition. Considerable variation in the timing of mitral valve closure, which means that it does not necessarily coincide with the onset of mechanical systole, has been described in the presence of raised left atrial pressure,[10 11] intraventricular conduction disturbances,[1-3] atrioventricular block,[4-6] and atrial fibrillation.[12] Since mitral valve closure must be the end of left ventricular filling its relation to the onset of systole is of considerable importance.

The study of patients with dual chamber pacemakers is of great interest. Firstly, these patients represent a unique physiological model in which the timing of cardiac events may be studied. The interval between the normal P wave and the ventricular pacing stimulus which it triggers when the pacemaker is in the VDD mode can be altered by reprogramming the pacemaker in the absence of any other physiological change. Therefore the effect of atrial and ventricular contraction on mitral valve closure and its relation to the onset of mechanical systole can be studied over a wide range of atrioventricular intervals. Secondly, study of these patients provides practical information about the atrioventricular interval that allows the longest diastolic filling period and thus the most efficient cardiac function.

### *Intraventricular conduction delay and the onset of systole*

The electromechanical delay, detected as the interval between the Q wave and the onset of the upstroke of the apex cardiogram, which coincides with the onset of left ventricular pressure rise,[7] was about 50 ms. This accords with previous reports.[13] In the paced patients we studied, this electromechanical delay lasted considerably longer (about 120 ms) and was the same for all three atrioventricular intervals. This delay may be partly because of slow initial spread of depolarisation from the right ventricular pacing site until it gains access to the faster specialised conducting system. If this is the case some increase in the electromechanical delay might be expected in the group of patients with left bundle branch block. This was not found by apex cardiography but other indicators suggest that a small delay does occur. Firstly, mitral valve closure was slightly delayed and is, as will be clear later, dependent on the onset of systole in these patients. Secondly, aortic valve opening, denoting the onset of left ventricular ejection was also delayed compared with values in normal individuals. Others have found a considerable delay of right ventricular contraction in right bundle branch block but they stated left ventricular contraction is not delayed in left bundle branch block because they claimed to have demonstrated normal timing of mitral valve closure.[2 3]

Their point of reference, however, was closure of the tricuspid valve. When we reanalysed their results with reference to the electrocardiographic Q wave we found a delay in mitral valve closure that is similar to that observed in the present study.

Despite the differences in the intervals between electrical and mechanical events in these three groups of patients (that is normal controls, patients with left bundle branch block, and patients with VDD pacemakers with an atrioventricular interval of 50 ms) the normal sequence of left ventricular pressure rise and mitral valve closure was maintained in all three groups. All three groups showed the same strong linear relation between the onset of systole and mitral valve closure. This clearly demonstrates the predominant effect of the onset of systole in closing the mitral valve and thus ending diastole in all three groups despite the increasing delay in the onset of systole due to impaired conduction in two of the groups.

The phases of the cardiac cycle are often defined with reference to the electrocardiogram with end diastole being taken as coinciding with the Q wave or pacing spike. By this definition the period of up to 127 ms after the pacing spike would be assigned to systole, despite the fact that the mitral valve is still open. In theory this period is long enough to permit all of rapid left ventricular filling[14 15] although in practice it is more commonly used for left ventricular filling due to atrial contraction. Similarly such traditional definitions of end diastole may cause considerable inaccuracy in the assessment of end diastolic left ventricular dimension by echocardiographic or scintigraphic techniques since some or all of the atrial contribution to ventricular filling will be neglected because it occurs after the Q wave. To avoid these problems we regard end diastole as occurring at the moment when the mitral valve closes, and the onset of systole as the moment when left ventricular pressure begins to rise.

### *Effect of various atrioventricular intervals on the end of diastole*

Each increase in the atrioventricular interval by 100 ms in the VDD paced patients made the coaptation of the mitral leaflets in relation to the pacing spike occur 50 ms earlier. This cannot be due to the mitral valve being closed earlier by left ventricular contraction, since the timing of the onset of systole in relation to the pacing spike did not change. The most likely explanation is that this was the result of a change in the mechanism causing mitral valve closure as the atrioventricular delay was increased. When the delay is short, closure is effected by ventricular systole, and this mechanism accords with the strong linear relation between the timing of the two events and the delay of 50 ms. At longer atrioventricular intervals atrial contraction may become the most important determinant of mitral closure. This concept is supported by echocardiographic studies of mitral closure in patients with complete heart block[4-6] in whom wide variations in the interval between atrial and ventricular contraction can be studied. It is suggested that atrial contraction raises left ventricular pressure so that as atrial systole ends there is a reverse pressure gradient which closes the valve unless ventricular systole intervenes to close it first. Therefore the mechanism of closure will vary depending on the atrioventricular interval.

In sinus rhythm a PR interval of more than 200 ms is required before mitral valve closure precedes ventricular contraction (that is as a result of atrial contraction).[16] The situation is different in patients with ventricular pacing. Movement of the valve at various atrioventricular intervals was studied by cinefluorography in a patient with a Starr-Edwards mitral prosthesis, complete heart block, and a ventricular pacemaker.[17] This showed that valve closure preceding ventricular systole occurred at much shorter atrioventricular intervals (>100 ms). Our study also shows that this effect often occurs when the interval is set at 150 ms. This difference between the interval required for atrial contraction to produce mitral closure in paced patients and those required in sinus rhythm is due to the longer delay in the onset of systole with reference to the electrocardiogram (pacing spike and Q wave respectively) in paced patients. This additional delay, which is approximately 80 ms, means that the functional atrioventricular interval lasts 80 ms longer in paced patients than it does in patients in sinus rhythm with the same electrocardiographic PR interval. Therefore, theoretically, atrioventricular delay settings of 50–100 ms should be sufficient to maintain the normal intervals between atrial and ventricular contraction in paced patients.

These observations are of considerable practical importance. An atrioventricular interval of 150 ms is commonly used when programming VDD pacemakers because this is erroneously thought to correspond to the functional interval in sinus rhythm. Our study, however, shows that at this setting mitral valve closure frequently occurred before the onset of ventricular systole, and thus late diastole was not available for ventricular filling. It is also commonly thought that short atrioventricular intervals lead to the atrial A wave being cut off prematurely by ventricular systole. This study shows that this is not the case. At a setting of 50 ms the onset of the mitral A wave occurred 5 (17) ms before the pacing spike. The delay of ventricular activation until 127 ms after the pacing spike allowed sufficient time for a mitral A wave of normal duration (132 ms) to occur at this setting. This value for the duration of the A wave is almost identical with that obtained from simultaneous left ventricular and left atrial tracings in patients with both normal and abnormal left ventricular function.[18] When the atrium and ventricle are paced sequentially, the delay between the atrial pacing spike and atrial activation, which may vary between 30 and 120 ms,[19] should be assessed individually and added to the proposed range of 50–100 ms advocated here for the VDD mode.

The reversed pressure gradient by which atrial contraction closes the mitral valve is determined by the force of atrial contraction.[4] It may be counteracted if atrial contraction is weak, atrial pressure is high, or if blood flow is increased. These additional influences may explain the wide individual scatter in the timing of mitral valve closure at long atrioventricular intervals. There were four patients in whom the timing of leaflet coaptation was unchanged despite increasing intervals. One had poor left ventricular function due to previous anterior myocardial infarction, and there was radiographic and clinical evidence of raised left atrial pressure. The other three were physically fit youths in whom the mitral valve reopened after the A wave. These four patients contribute to the exceptional individual values seen in Fig. 8.

Although in this study we examined only the sequence of haemodynamic events in the left side of the heart, there is no evidence that the sequence in the right heart is essentially different. It is well known that the right atrial P wave occurs about 30 ms before depolarisation of the left atrium. Phonocardiographic[3] and invasive studies[2] of patients with left bundle branch block or right ventricular pacemakers have shown that the onset of contraction of both ventricles is simultaneous. Thus the selection of the short atrioventricular interval, shown in this study to benefit left ventricular filling, is unlikely to affect right ventricular function in an adverse way.

### *Left ventricular filling time*

Left ventricular filling time was significantly shortened in our patients with VDD pacemakers when the atrioventricular delay was set at 150 ms or longer. When the delay was 150 ms filling time was reduced by 60 ms and this reduction increased to 130 ms when the delay was set at 250 ms. Timing of mitral valve opening was the same at all atrioventricular intervals. With an atrioventricular delay of 150 ms left ventricular filling time was reduced by a combination of reduced cycle length and earlier mitral valve closure. With an increase of the programmed delay to 250 ms the further reduction in filling time was entirely due to even earlier mitral valve closure since the cycle length remained constant. The resulting interval between mitral valve closure and the onset of left ventricular systole of up to 100 ms serves neither left ventricular filling nor ejection.

This waste of time may be harmless at a normal heart rate and with a normal left ventricle because up to 80% of the left ventricular filling occurs during the initial rapid filling phase of diastole which lasts about 120 ms and the remaining 20% can easily be completed during diastasis and with atrial contraction. Elderly pacemaker patients, however, may have other cardiac abnormalities such as ischaemic heart disease or left ventricular hypertrophy that lead to disturbed left ventricular diastolic function. Seven of our 19 patients with VDD pacemakers had evidence of such abnormality with delayed mitral valve opening consistent with left ventricular relaxation abnormalities. In these circumstances the amount of left ventricular inflow during the early rapid filling period is reduced to 60% or less and thus the time available for left ventricular filling in late diastole becomes far more important and may determine the left ventricular end diastolic volume and stroke volume.

The wasted time in late diastole with long atrioventricular intervals also becomes important during exercise, particularly in the presence of abnormal left ventricular diastolic function when the heart rate increases and left ventricular filling time is reduced. Since left ventricular filling time is strongly dependent on cycle length, we analysed this relation in all groups (Fig. 7). The regression equations were identical for the normal controls, patients with left bundle branch block, and VDD pacemaker patients with an atrioventricular interval of 50 ms. These equations show that theoretically left ventricular filling time would be zero at mean cycle length of 320 ms. The relation between cycle length and filling time was shifted downwards as atrioventricular intervals increased. Thus with an atrioventricular interval of 250 ms the cycle length producing a theoretical filling time of zero increases to 405 ms. Therefore longer atrioventricular intervals have an increasingly greater negative influence on filling time as heart rate increases. We conclude that a short atrioventricular interval of 50 or 75 ms in patients with VDD pacemakers is likely to promote more physiological conditions by maximising left ventricular filling time both at rest and on exercise. This is likely to be of particular benefit in the groups of patients who most need this type of pacemaker; the young who require high cardiac outputs at high heart rates and patients with impaired left ventricular diastolic function.

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# Auscultatory characteristics of normally functioning Lillehei-Kaster, Björk-Shiley, and St Jude heart valve prostheses

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SUMMARY Auscultatory and echocardiographic and phonocardiographic studies were performed on 26 patients who had a total of 11 Lillehei-Kaster, 16 Björk-Shiley, and 18 St Jude heart valve prostheses functioning normally in the aortic or mitral positions or both. With all types and positions of prostheses a distinct closing sound was always detected. It was frequently heard in two parts which, according to echocardiographic and phonocardiographic studies, resulted from the onset and completion of the valve closure. An opening sound could be heard from all Björk-Shiley and St Jude valves but from only four of the 11 Lillehei-Kaster valves. The opening sounds due to mitral prostheses consisted of two to three closely spaced clicks detected as a faint early diastolic crackle on auscultation. Echocardiography with phonocardiography indicated that they were related to the onset and termination of the disc opening excursion. In the aortic position the valves always produced early to mid-systolic murmurs, and a soft early diastolic murmur was also heard in seven of 23 patients. A mid-diastolic rumble was heard in 12 of 22 patients with mitral prostheses.

Normally functioning tilting disc valve prostheses produce characteristic auscultatory findings, and familiarity with these findings will be useful in clinical evaluation of patients with these prostheses.

The development and adoption of more and more sophisticated diagnostic techniques may have overshadowed the value of simple clinical skills in cardiology. The latest trends in the assessment of prosthetic heart valve function are an example of this. Although cardiac auscultation was used to evaluate the ball-in-cage valves of the 1960s,[1] non-invasive studies of the more recently introduced tilting disc valves have relied mainly on echocardiography and phonocardiography,[2-4] cinefluoroscopy,[5 6] or Doppler echocardiography.[7 8] Not one original investigation describes in detail the valves' auscultatory characteristics. Yet, as Mintz *et al* have shown,[9] careful auscultation may be more sensitive and more specific than echocardiography and phonocardiography or cinefluoroscopy in detecting prosthesis malfunction. To identify an abnormality the clinician must become familiar with the range of normal findings associated with the most commonly used prosthetic valves.

We describe the auscultatory characteristics of normally functioning Lillehei-Kaster, Bjork-Shiley, and St Jude prostheses in a group of patients who had had uneventful double valve operation at our hospital. To confirm and explain the auscultatory observations we also present the relevant echocardiographic and phonocardiographic findings in these patients.

## Patients and methods

The study group consisted of 26 patients (nine men and 17 women; mean age 56 years, range 32–69) who had normally functioning uni-leaflet or bi-leaflet tilting disc valve prostheses in the aortic or mitral

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Accepted for publication 18 November 1985

positions or both. They were examined in July–August 1983, a mean of 37 months after operation (range five months to 10 years). Routine physical examination, 12 lead electrocardiogram, chest *x* ray, and laboratory tests were also performed. Prosthetic valve function was judged to be normal if there had been (*a*) an uncomplicated postoperative course; (*b*) no embolic episodes; (*c*) no clinical signs or symptoms of prosthesis obstruction or paravalvar regurgitation; (*d*) no haemolytic anaemia; and (*e*) normal movements of the valve disc(s) on echocardiography, provided the examination was of technically acceptable quality. Most patients had undergone double valve replacement and a total of 45 tilting disc valve prostheses had been implanted, 23 in the aortic and 22 in the mitral position. These included 11 Lillehei-Kaster, 16 Björk-Shiley, and 18 St Jude valves. At the time of our study 13 patients were in sinus rhythm and 13 had atrial fibrillation.

### AUSCULTATION

We performed cardiac auscultation over different areas of the chest wall using both the diaphragm and the bell of the stethoscope and with the patient in the supine, left lateral, and sitting positions. We noted the quality, intensity, and variation of the prosthesis clicks as well as of the site at which they were loudest. We also noted the quality, intensity, localisation, and duration of any systolic or diastolic murmur.

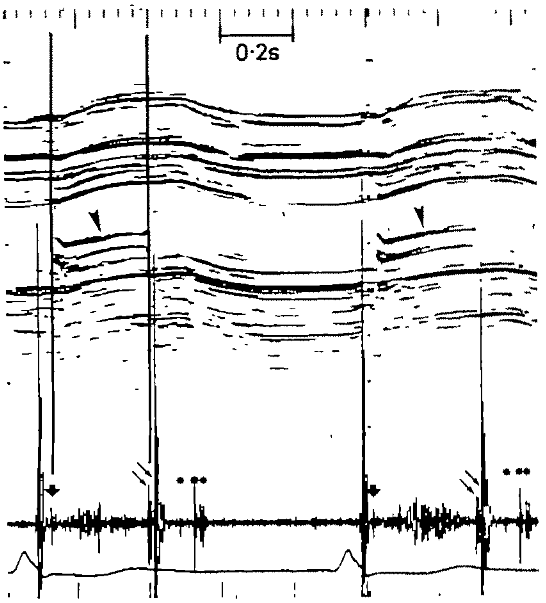


Fig. 1 *Echophonocardiogram of a Lillehei-Kaster aortic valve prosthesis showing the motion of the disc (arrowheads) within the aortic root and the simultaneous phonocardiogram and electrocardiogram (bottom of the figure). The phonocardiogram shows one opening click (thick arrows), two closing clicks (thin arrows), and an ejection type systolic murmur. The vertical lines show the timing of the clicks in relation to the disc movements. The patient also had a Bjork-Shiley mitral valve which produced three early diastolic clicks (asterisks) on opening.*

### PHONOCARDIOGRAPHY AND ECHOCARDIOGRAPHY

The phonocardiographic recordings were made by means of a suction type IREX heart sound microphone and the fibreoptic strip chart recorder in an IREX System III echocardiograph. The microphone was placed over the site of the peak auscultatory intensity of the sound or murmur of interest not on any standard phonocardiographic area. The filter settings were chosen according to whether prosthesis clicks and high frequency murmurs or low frequency mitral murmurs were to be recorded. The chart speed was 100 mm/s.

The echocardiographic studies were performed with the IREX System III echocardiograph equipped with a medium focused 2·25 MHz, 0·5 inch transducer. The aortic valve studies were made either from the left parasternal area or from the right supraclavicular fossa, and the mitral studies from both the left parasternal and apical areas. Once the motion of the valve disc(s) was clearly seen on the M mode screen it was recorded on dry silver paper simultaneously with an electrocardiogram and a phonocardiogram (see above) at a speed of 100 mm/s. Satisfactory echocardiograms were obtained from 17 of the 23 aortic valve prostheses and from 19 of the 22 mitral prostheses. The recordings were scrutinised visually to determine the timing of the valve clicks in relation to the movements of the disc.

## Results

### LILLEHEI-KASTER VALVE

The 11 Lillehei-Kaster valves were all in the aortic position. A single, low intensity opening click was heard in four patients and in another four the click could be recorded but not heard (Fig. 1). The closing sound invariably consisted of two parts, a sharp low intensity component and a high intensity metallic click (Fig. 1), that were readily distinguishable by attentive auscultation. A grade 2–3/6 ejection systolic murmur was heard in all patients. It usually filled most of systole, peaked at or slightly before mid-systole, and was quite harsh in some patients (Fig. 1). A palpable thrill was noted in one patient. A short early diastolic high frequency murmur of grade 1–2/6 intensity was detected in four patients on auscultation but not on phonocardiography.

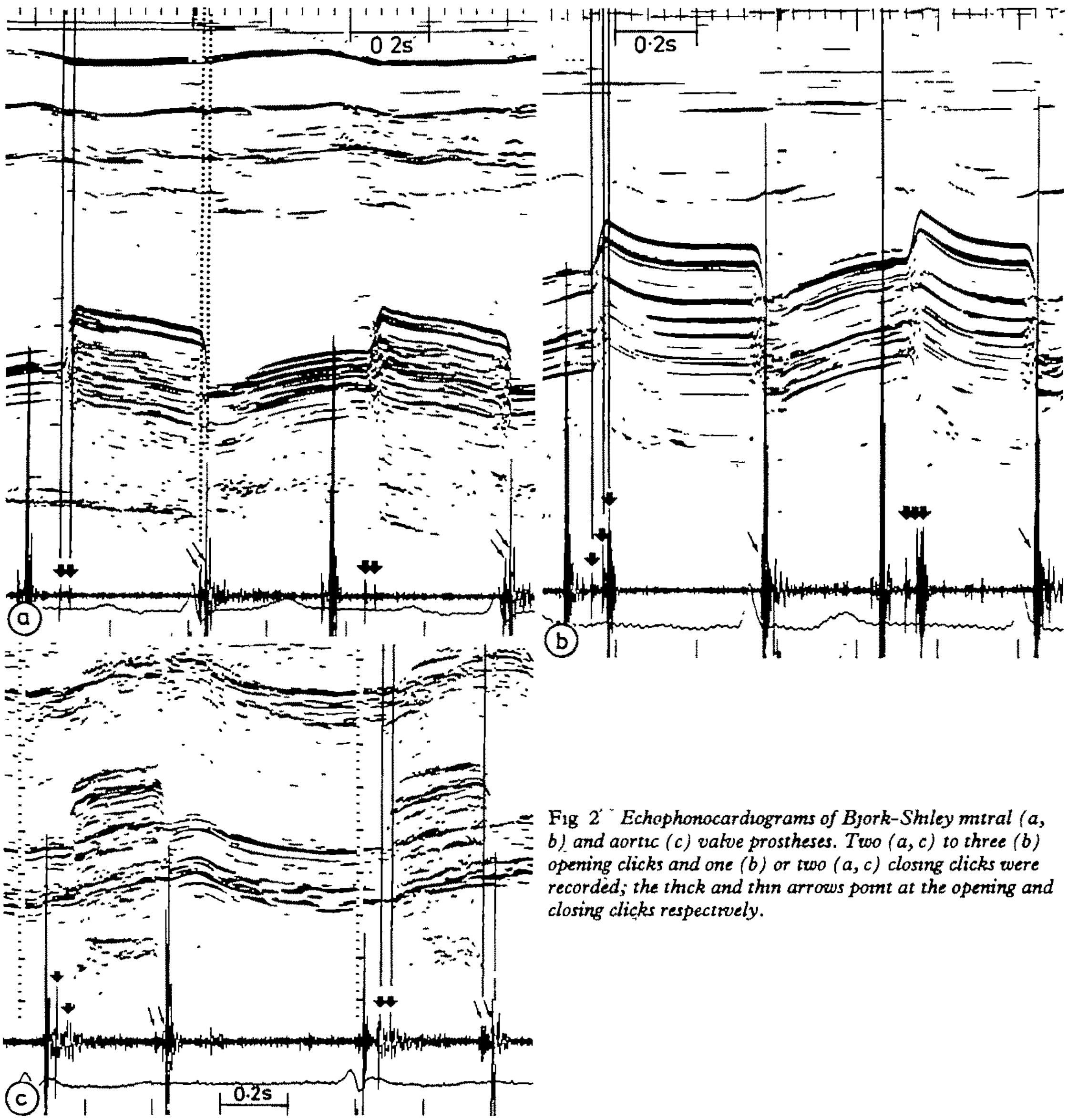


Fig 2 *Echophonocardiograms of Bjork-Shiley mitral (a, b) and aortic (c) valve prostheses. Two (a, c) to three (b) opening clicks and one (b) or two (a, c) closing clicks were recorded; the thick and thin arrows point at the opening and closing clicks respectively.*

BJÖRK-SHILEY VALVE

There were 15 Björk-Shiley valves in the mitral position. Both opening and closing sounds were invariably audible. The opening sound consisted of several sharp but faint clicks which produced a characteristic crackling sound in early diastole. Phonocardiography showed that there were two to three closely spaced opening clicks in each patient (Fig. 2a and 2b). The closing sound was usually heard as a single intense click (Fig. 2b), but a second minor click was distinguishable before the major closing sound in five patients (Fig. 2a). A grade 2/6 rumbling mid-diastolic murmur was heard and recorded in eight of 15 patients (Fig. 3).

One patient had a Björk-Shiley valve in the aortic position. Both the opening and closing sounds were heard in two parts, and a short grade 2/6 early systolic murmur was detected as well (Fig. 2c).

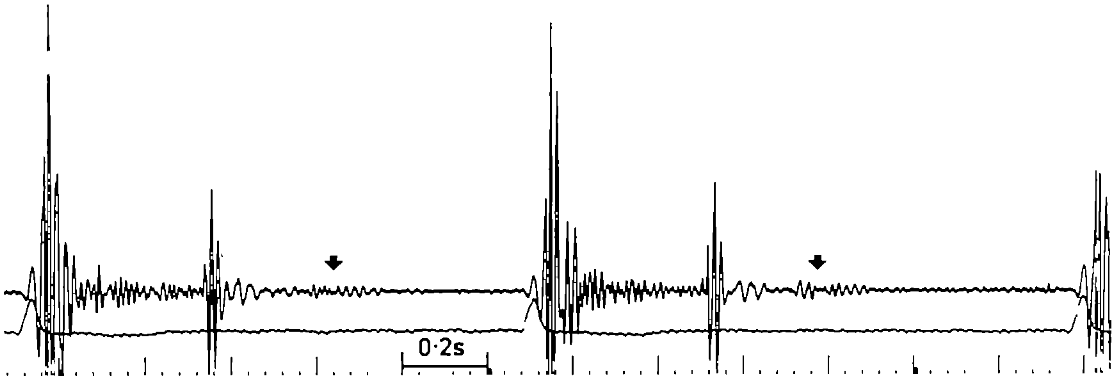
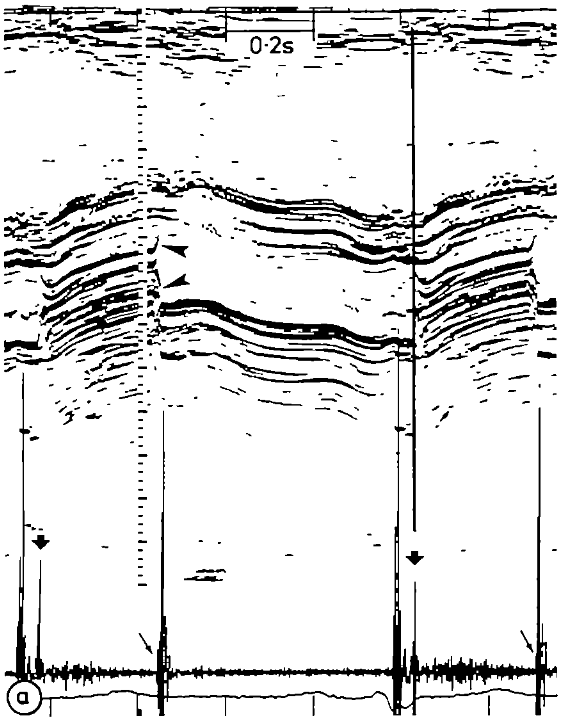


Fig 3 *A low frequency phonocardiogram showing the mid-diastolic rumble (arrow) in a patient with a Bjork-Shiley mitral valve prosthesis. The rhythm is slow atrial fibrillation*



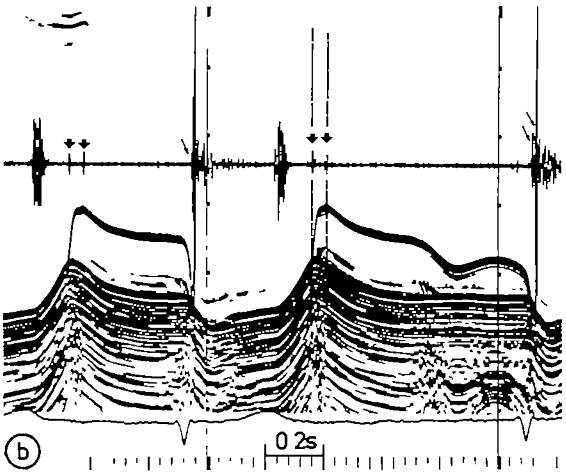


Fig. 4 *Echophonocardiograms of St Jude aortic (a) and mitral (b) valve prostheses. The aortic valve produces one opening click and one closing click (a) whereas the mitral valve gives rise to two clicks on opening and one to two on closing (b). The opening and closing clicks are indicated by the thick and thin arrows respectively. The arrowheads show the two echoes from the leaflets of the aortic valve (a). The mitral valve recording was made at an apical transducer position and therefore the motion of one leaflet only is seen (b).*

## ST JUDE VALVE

There were 11 St Jude valves in the aortic position. An opening sound was always heard, usually as a single low intensity click (Fig. 4a), but two clicks were detectable in one patient (Fig. 5). The closing sound typically had two components (Fig. 5), but in two patients only one, high intensity click was found (Fig. 4a). A grade 2/6 short and soft early to mid-systolic murmur was heard in all patients and a grade 1–2/6 early diastolic murmur in three.

Seven patients had a St Jude valve in the mitral position. A faint, crackling opening sound was heard on careful auscultation in all. Phonocardiography showed that the sound was composed of two or, rarely, three separate clicks of low intensity (Figs. 4b and 5). The closing sound was single in four patients

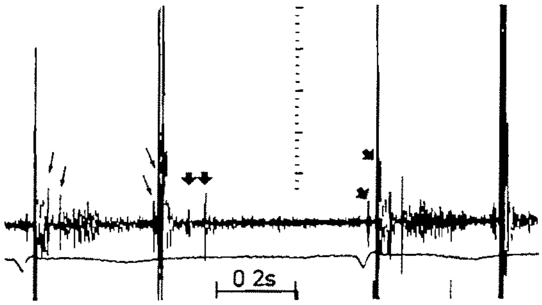


Fig. 5 *A high frequency phonocardiogram of a patient with aortic and mitral St Jude valves. Note the double opening and closing clicks from both the aortic (thin arrows) and mitral (thick arrows) valve prostheses.*

and had two distinct components in three (Fig. 5). A grade 2/6 mid-diastolic rumble was heard and recorded in four patients.

GENERAL OBSERVATIONS

The aortic valve clicks were heard best in the middle or lower left parasternal area. Also the mitral valve clicks were usually best distinguished in this area and only exceptionally over the cardiac apex. The intensity of both aortic and mitral valve opening sounds varied with respiration in some patients; their audibility was greatest at end expiration. The intensity of the mitral valve closing sound varied inversely with the duration of the preceding diastole in patients with atrial fibrillation. After prolonged pauses the normal closing sound of the Björk-Shiley valve, but not that of the bi-leaflet St Jude valve, was on occasion absent and was replaced with a faint late diastolic crackle that indicated presystolic valve closure (Fig. 6).

The diastolic murmurs produced by the mitral Björk-Shiley and St Jude valves were similar in quality, intensity, and duration and resembled the rumble of mild native valve mitral stenosis save for the lack of a presystolic component even in patients in sinus rhythm. The murmur could be accurately localised to the apical area and was most easily detected when the patient lay in the left lateral position. The systolic murmurs from the aortic prostheses were best heard in the left parasternal area. They were of an "innocent" nature in all patients with a St Jude aortic prosthesis but resembled mild native valve aortic stenosis in several patients with Lillehei-Kaster valves. Neither the presence nor the intensity of systolic or diastolic murmurs correlated with the prosthetic valve size.

The timing of the prosthetic valve clicks in relation to the disc movements on echocardiography was the same irrespective of the type or position of the prosthesis. Single opening or closing clicks coincided with the onset of the disc opening motion or with the completion of its closure. When multiple clicks were detected, both the onset and the termination of the disc opening or closing excursion had their audible and recordable counterparts (Figs. 1, 2, 4, and 6).

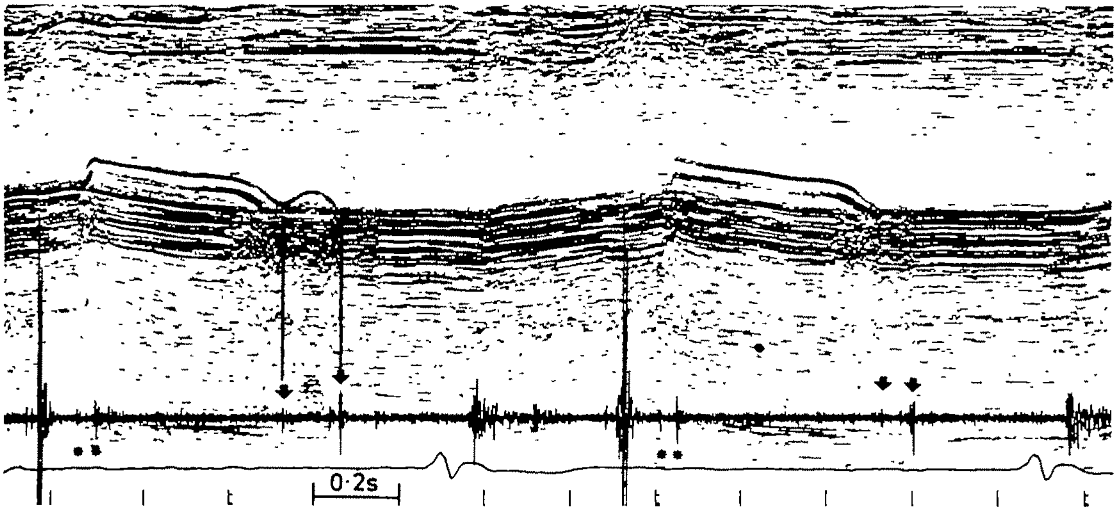


Fig 6 *Echophonocardiogram of a Bjork-Shiley mitral valve in a patient who had slow atrial fibrillation Note the presystolic valve closure and simultaneous small clicks (arrows) on the phonocardiogram. Two opening clicks are also recorded (asterisks).*

## Discussion

CLICKS

It is well known that the tilting disc valve prostheses produce closing sounds which are distinct and easily detectable during routine cardiac auscultation.[10] Their attenuation or loss in serial examinations indicate prosthesis malfunction, usually thrombosis or tissue ingrowth.[11 12] The present study adds to this knowledge by showing that irrespective of the type or position of the prosthesis the normal closing sound may be heard and recorded in two parts produced by the onset and termination of the disc closing excursion. In theory, loss of a previously detectable minor component of a closing sound could be the first signal of incipient valve thrombosis, but as yet we have no positive evidence to support this.

According to recent authoritative reviews,[10 13] the tilting disc valves produce little or no sound on opening. This belief is based on a few reports[2 4 14 15] which focused on echocardiographic examination and paid less attention to the details of phonocardiography, and often made no mention of auscultatory findings.[4 14 15] We have showed that apart from the Lillehei-Kaster valve, which can open silently, normally functioning tilting disc valves invariably produce audible and recordable sounds on opening. Furthermore, the opening sound may contain multiple clicks, particularly when the valve is in the mitral position. Smith *et al*, Feldman *et al*, and Raizada *et al* also found recordable opening clicks in patients with St Jude valve prostheses.[10 16 17] According to Smith *et al* the opening click of the St Jude aortic valve is recorded only after complete opening of the leaflets and is caused by turbulent transvalvar flow.[10] We did not confirm their observation and cannot agree with their theory because we found that the opening clicks of the St Jude valve coincided either with onset alone or with onset and termination of the opening motion of the valve leaflets (Fig. 4). The clinical importance of tilting disc valve opening sounds has not been established, but some reports suggest that alterations in the opening sound may be an even more sensitive indication of evolving valve thrombosis than alterations in the closing sound.[18 19]

MURMURS

Recordable murmurs are common in patients with normally functioning tilting disc valve prostheses. Gibson *et al* found mid-diastolic rumbles in 14 of 20 patients with Lillehei-Kaster mitral valves,[2] and DePace *et al* recorded similar murmurs in six of 28 patients with St Jude mitral prostheses.[4] In the present study, a rumbling mid-diastolic murmur was easily *heard* in more than 50% of patients with mitral valve prostheses and a systolic ejection type murmur was heard in all patients with aortic prostheses. These "normal" murmurs indicate turbulent flow and may partly result from the small pressure gradients present across all types of artificial valves.[20] Any prolonged diastolic mitral rumble or a delayed peak systolic aortic valve murmur are abnormal and suggest prosthesis obstruction.[19] The systolic murmur produced by the Lillehei-Kaster prosthesis in the aortic position was clearly more intense and longer in duration than that produced by the St Jude at the same site. This can be accounted for by the higher pressure gradients measured across the Lillehei-Kaster valve in the aortic position.[20]

Evidence from the present study supports the view that short early diastolic murmurs may sometimes be heard in patients with apparently normally functioning tilting disc aortic valve prostheses.[10] These murmurs result from the mild regurgitation permitted by the valve design.[20] Any murmur extending into the latter half of diastole or associated with other signs of aortic insufficiency should arouse suspicion of paravalvar regurgitation. Although tilting disc mitral valve prostheses may generate soft systolic murmurs,[2] their normal auscultatory characteristics do not include a pansystolic mitral regurgitant murmur of any intensity.

## Conclusions

Normally functioning Lillehei-Kaster, Bjork-Shiley, and St Jude heart valve prostheses generate characteristic and easily recognisable auscultatory findings. Distinct and frequently double clicks are heard on valve closing and, apart from the Lillehei-Kaster valve which not uncommonly opens silently, these valves also regularly produce audible sounds on opening. Multiple opening clicks do not indicate prosthesis malfunction. In the aortic position these valves always give rise to early or mid-systolic murmurs, and on occasion a short early diastolic murmur may be heard as well. Mitral valve prostheses produce mid-diastolic rumbles in more than half the patients. Familiarity with these normal findings should help clinicians to take full advantage of the auscultatory findings when examining patients with these prostheses.

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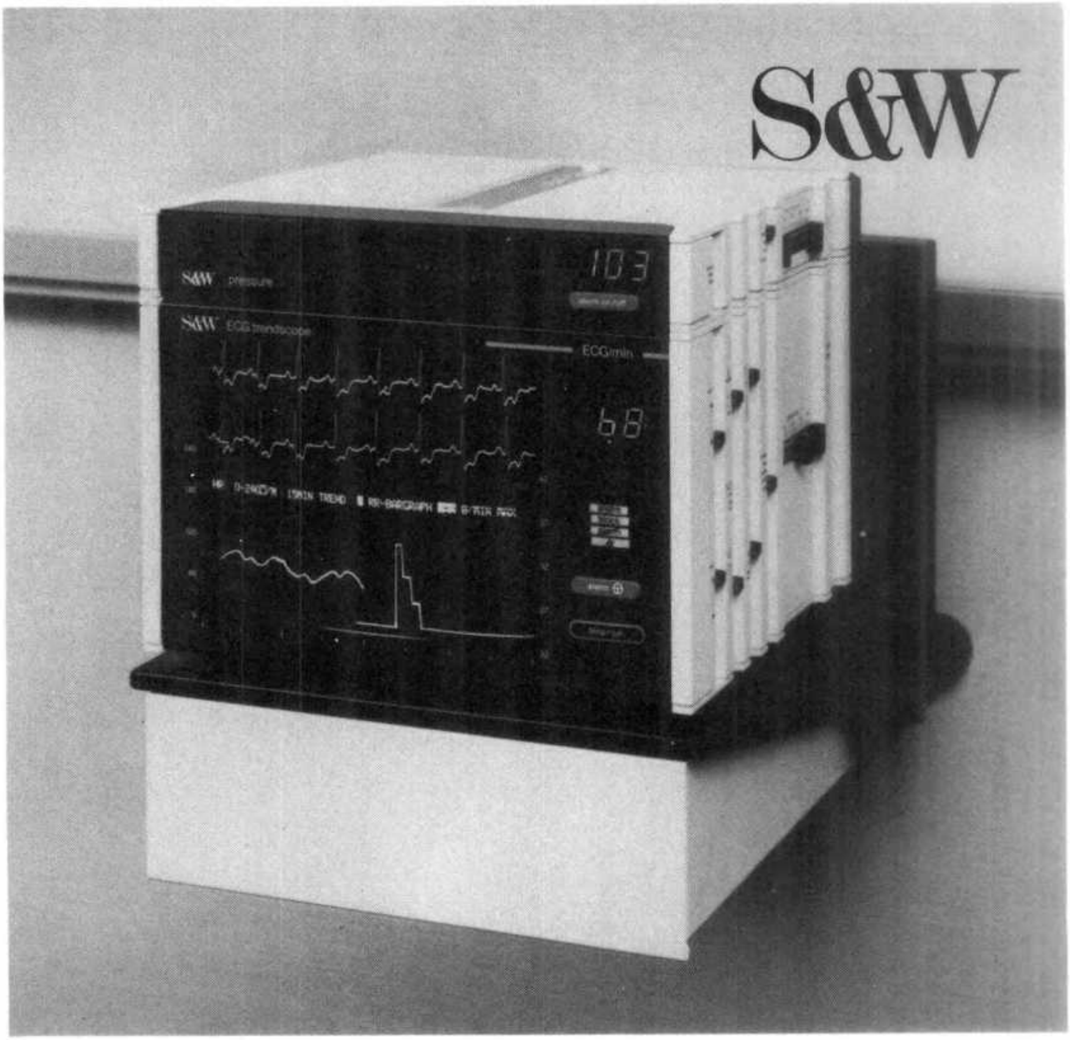

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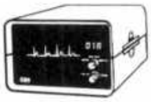

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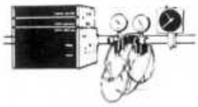

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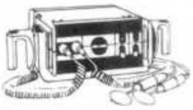

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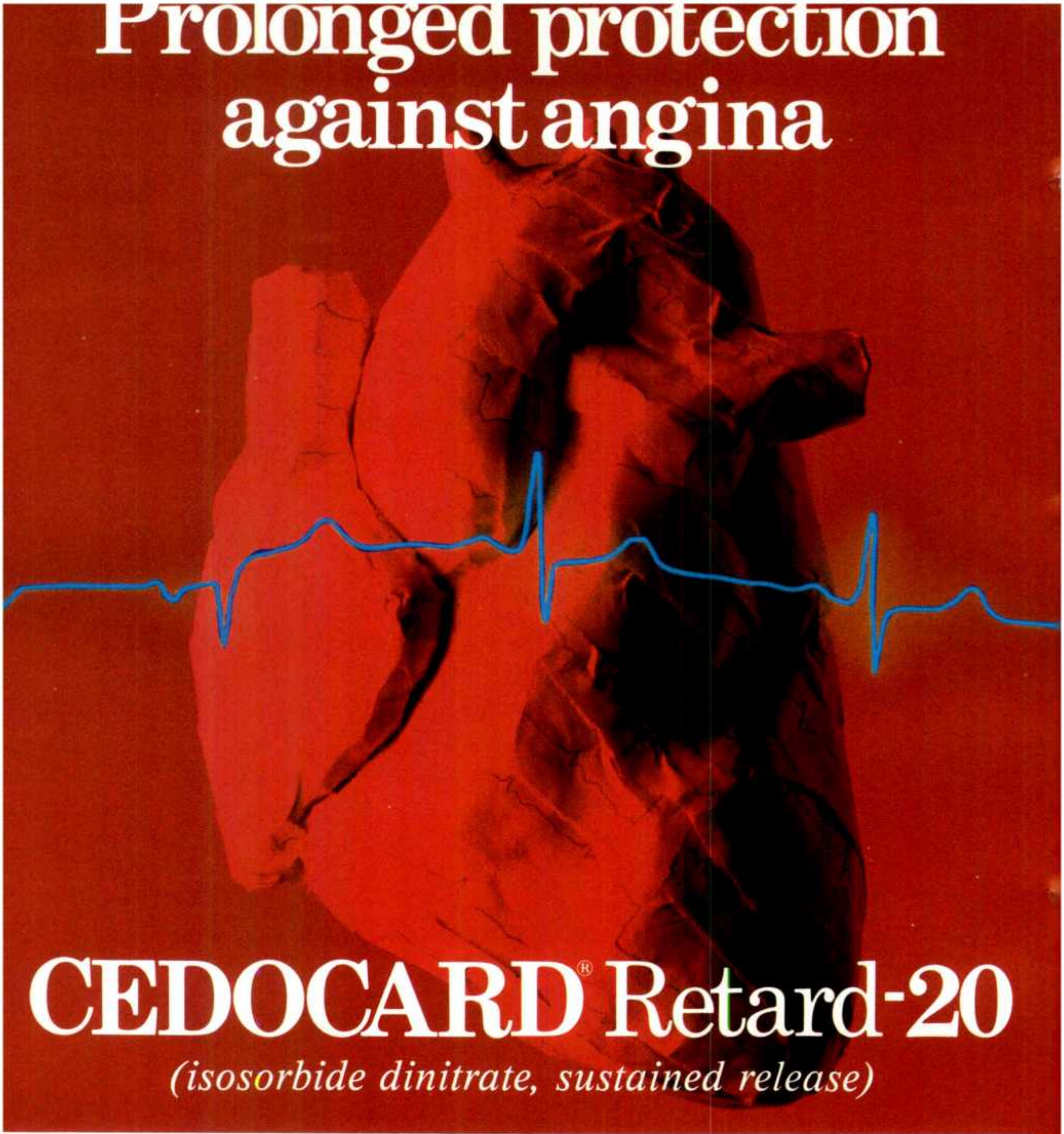
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# Late results of right ventricular outflow tract reconstruction with Björk-Shiley valved conduits

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SUMMARY Between 1971 and December 1976, 27 children with congenital heart disease underwent right ventricular outflow tract reconstruction with conduits incorporating a Björk-Shiley valve. The conditions corrected were pulmonary atresia with ventricular septal defect (14 patients), truncus arteriosus (6 patients), and complex disease (7 patients). At operation the children were aged from 12 days to 16 years (five patients were less than one year old). Overall mortality for the group was high (52%). There were nine early deaths and five late ones. Actuarial survival till death or reoperation was 55% at four years, 35% at eight years, and 28% at 12 years. Ten children subsequently underwent reoperation for conduit stenosis caused by neointimal proliferation and valve obstruction. The new conduits incorporated a biological valve.

Mortality was highest in patients aged less than one year, and in those with truncus arteriosus, severe pulmonary hypertension, or complex heart disease. Mechanical valves should be avoided in conduit reconstruction of the right ventricular outflow tract for congenital heart disease.

In 1971 we started to use a Björk-Shiley tilting disc aortic valve prosthesis incorporated into a Dacron vascular graft for the repair of various complex cardiac malformations including pulmonary atresia, transposition of the great arteries with ventricular septal defect, and truncus arteriosus. Initial experience with this valved conduit was promising; there was no valve dysfunction for up to three years postoperatively.[1]

We now present our long term experience with this conduit in 27 children.

## Patients and methods

Between March 1971 and December 1976, 27 children underwent right ventricular outflow tract reconstruction with Björk-Shiley valved conduit. Fourteen children with pulmonary atresia and ventricular septal defect underwent repair. Six infants with truncus arteriosus also had conduit reconstruction of the right ventricular outflow tract. Other forms of complex congenital disease were also repaired by this technique including tetralogy of Fallot, double outlet right ventricle, single ventricle, and transposition of the great arteries with ventricular septal defect (Table 1).

Seventeen (63%) of the children had had previous systemic to venous shunts in an attempt to relieve cyanosis and promote growth in the pulmonary circulation (Blalock-Taussig eight patients, Waterston seven patients, Potts two patients). Pulmonary artery banding had been performed to reduce the pulmonary circulatory flow in two infants with truncus arteriosus.

Table 1 *Indications for valve implant in 27 patients*

| *Indication* | *No* |
|---|---|
| Truncus | 6 |
| TGA with VSD | 1 |
| Pulmonary atresia with VSD | 14 |
| Tetralogy of Fallot | 1 |
| Complex: DORV | 2 |
| Taussig-Bing | 1 |
| Single ventricle | 2 |

TGA, transposition of the great arteries; VSD, ventricular septal defect; DORV, double outlet right ventricle.

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Accepted for publication 18 November 1985

Patients were aged from 12 days to 16 years. Five (18%) children were aged less than one year at operation.

TECHNIQUE

Routine cardiopulmonary bypass with hypothermic circulatory arrest was performed in all patients. We have described this technique elsewhere.[1 2] The Björk-Shiley prosthesis was fixed into the conduit during the period of core cooling, usually by means of a continuous suture technique. We used twenty three straight tubular grafts, ranging from 16 to 28 mm in diameter, and four bifurcation grafts. The valve prosthesis size ranged from 17 mm to 27 mm, and valves with pyrolytic carbon discs were used in all except one of the patients. Twenty one (77%) children had a valve size ⩾21 mm.

After systemic cooling to 17–18°C repair was performed during a period of circulatory arrest which lasted from 15–77 minutes (mean 57 minutes).

We opened the right ventricular outflow (usually longitudinally or parallel to major coronary branches), avoiding damage to major coronary arteries. Ventricular septal defects were closed with a patch of Dacron. The conduit was then cut to length and the distal anastomosis was performed either to the main pulmonary artery, when this was present, or to the confluence of right and left pulmonary arteries. In two patients the bifurcation grafts had to be anastomosed separately to each pulmonary artery, leaving the division of the graft astride the ascending aorta (truncus).

The proximal anastomosis was constructed after the graft end had been cut obliquely to allow the graft to assume a gentle curve after it had been sutured to the right ventricle; this was done to prevent conduit compression or distortion after sternal closure. Warfarin anticoagulation was not routinely used in all patients.

## Results

MORTALITY

*Early*—Nine children died at or soon after operation (Table 2). Three children, all with truncus II, aged less than 4 months died at operation; two of them were moribund before operation. One child with pulmonary atresia and ventricular septal defect died after unrecognised injury to the left anterior descending artery. No death was due to valve dysfunction.

*Late*—Five children died more than 30 days after operation (Table 2). Two children (with double outlet right ventricle and pulmonary atresia with ventricular septal defect) died suddenly at 3 months and 3½ years respectively, presumably from an arrhythmia. In both cases the valved conduit was examined at necropsy and found to be functioning adequately.

One child (with pulmonary atresia and ventricular septal defect) underwent reoperation four years later because of intimal flap proliferation and conduit stenosis. This child subsequently died at a second reoperation procedure (for a failed Hancock bioprosthesis) eight years after the original operation. Another child (pulmonary atresia with ventricular septal defect) died suddenly at recatheter study for right ventricular outflow tract obstruction (six years after operation). Necropsy showed a massive neointimal prolapse and acute Björk-Shiley valve obstruction.

Actuarial survival till death or reoperation was 55% at four years, 35% at eight years, and 28% at 12 years (Fig. 1).

REOPERATION

Of the 18 children who survived operation, 10 (55%) subsequently underwent reoperation for right ventricular outflow tract obstruction. All these children had important neointimal proliferation in the conduit; in two children the Björk-Shiley valve was both partly obstructed and fixed in a semi-open position.

In five children the new conduit contained a Hancock bioprosthesis (usually a 25 mm one). The remaining five had Carpentier-Edwards porcine bioprostheses (range 22–25 mm). Of the patients undergoing reoperation, two subsequently had further repeat operations. One child (pulmonary atresia with ventricular septal defect) died at reoperation for right ventricular outflow tract obstruction in a Carpentier-Edwards conduit; the other child (pulmonary atresia with ventricular septal defect) also underwent successful replacement of a Hancock prosthesis with a Carpentier-Edwards bioprosthesis because of staphylococcal endocarditis.

Only four patients are still alive with the original Björk-Shiley valve conduit in situ. Two of these have mild degrees of right ventricular outflow tract obstruction, with slightly increased right ventricular pressures (16–20 mm) at restudy.

## Discussion

Both valved and non-valved conduits have been used successfully for right ventricular outflow tract reconstruction.[3-7] Our group of 27 children undergoing right ventricular outflow tract reconstruction with a Björk-Shiley valved conduit represents a unique long term experience of a mechanical valve in this position.

The size of the Björk-Shiley valves ranged from

Table 2 *Early and late mortality in children undergoing operation*

| *Pathology* | *Age at operation* | *Cause* |
|---|---|---|
| Early mortality (n = 9): | | |
| Truncus | 12 days | Low output |
| Truncus | 3 mnth | Low output |
| Truncus | 4 mnth | Low output |
| Truncus | 6 yr | Pulmonary oedema |
| Pulmonary atresia/VSD | 4 yr | LAD injury |
| Pulmonary atresia/VSD | 4 yr | Low output |
| Single ventricle | 12 yr | Low output |
| Single ventricle | 16 yr | Low output |
| DORV | 5½ yr | Atrioventricular dissociation |
| Late mortality (n = 5): | | |
| Pulmonary atresia/VSD | 1 yr | Pulmonary hypertension |
| Pulmonary atresia/VSD | 2 yr | ? Arrhythmia |
| Pulmonary atresia/VSD | 5 yr | Two repeat operations |
| Pulmonary atresia/VSD | 7 yr | Valve obstruction |
| DORV | 13 yr | ? Arrhythmia |

VSD, ventricular septal defect; DORV, double outlet right ventricle; LAD, left anterior descending coronary artery.

17 to 27 mm. Most of the valves implanted (21 patients) were in sizes consistent with adult needs (size 21 mm), and would certainly be adequate for growth of the patients. Although the children were not routinely anticoagulated, valve thrombosis or pulmonary embolism was not clinically apparent.

Mortality for the whole group was high (52%). Actuarial survival (till death or reoperation) was 55% at four years and 28% at 12 years. Operative mortality was high (33%), but, bearing in mind the severity of disease, the age of the patients, and the lack of sophisticated techniques of myocardial preservation (except deep hypothermia) when these operations were done, the results are not unreasonable. Early mortality was worst for children with truncus (four cases) or complex disease (three cases) and those in whom pulmonary hypertensive disease (four cases) was developing. Although the relation between mortality and age at operation is not statistically significant for the total group, three (60%) of five patients aged $\leq 1$ year died at or soon after operation.

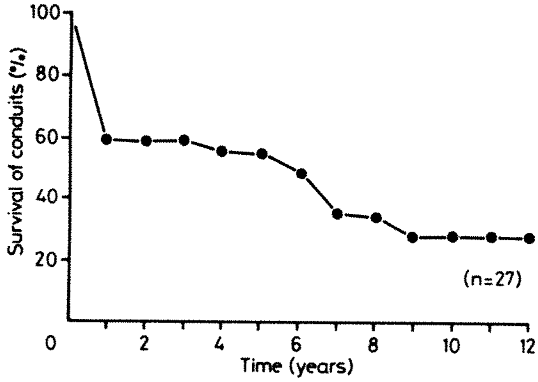

Fig. 1 *Actuarial survival till death or reoperation for patients after right ventricular outflow tract reconstruction with conduits with Björk-Shiley valves.*

The development of stenosis of the valved conduit and the need for catheter restudy was established clinically by an increase in fatigue, a pulmonary outflow murmur of increasing intensity, and signs of right ventricular overactivity or failure. Some workers have suggested that catheter restudy should be routinely performed after operation as an objective measure of pulmonary tract stenosis.[4 5 8–10]

Heck *et al* have reported catheter data obtained one year or more after operation; 57% of their patients had a moderate to severe pressure gradient across the valved conduits at catheter restudy (both homograft and heterografts), despite the fact that 88% of them were symptom free.[8] We feel that some caution should be exercised. One patient in our series had a sudden fatal valve obstruction after the neointimate peel had been dislodged at catheter restudy. The peel is often only tenuously attached to the Dacron conduit[6–8 11–13] and is easily detached and may lead to acute valve obstruction or massive pulmonary embolism. We now routinely assess the outflow tract by means of cross sectional echocardiography before catheter restudy.

Recurrent or residual valved conduit obstruction has many causes: conduit compression, valve stenosis or obstruction, and the development of a neointimal peel causing conduit stenosis. Bailey *et al* reported that conduit compression between sternum and heart was the commonest cause of right ventricular outflow tract obstruction in their patients (five of 68 patients).[14] We have not experienced this difficulty in our patients.

The frequency of conduit compression has decreased considerably in later series and this has been due to improvement in surgical technique.

Compression is best avoided by siting the valve as far distally as possible[15] and by having the conduit in a reversed "C" location in the mediastinum—to the left with levocardia and to the right side with dextrocardia and levoposition of the aorta.[14–16] Removal of the posterior table of the sternum has also been suggested, but this should not be necessary if the conduit has been well orientated laterally by the above technique.[16] None the less whatever technique is used, there seems to be evidence that conduit compression may be related to growth of the heart or to ventricular hypertrophy.[8]

Valvar stenosis or obstruction is common in those conduits that incorporate a heterograft or homograft. Agarwal *et al* reported that porcine valvar stenosis was the commonest cause of obstruction in their series (38%).[11] In almost all reported series, obstruction has been mainly due to calcific valvar stenosis.[9 17–22] Calcific stenosis is a well known complication of aortic homografts in the pulmonary position, but this stenosis mainly affects the wall of the homograft and later the valve leaflets. Excellent long term results with aortic homografts for right ventricular outflow tract reconstruction have recently been reported by Ross and Somerville; they reported a low late reoperation rate (11·5%) for conduit stenosis (at 10 years) in three of 26 patients followed for more than 10 years.[23] Stark *et al* use an aortic homograft as their conduit of choice for the right ventricular outflow tract and they have noted a similar low late reoperation rate (16 out of 170, 9·4%.[24] Both groups also implicate the Dacron patch that is used to bridge discontinuity between the homograft and the right ventricle as the cause of obstruction by a neointimal peel. This problem can be avoided by use of an aortic homograft with its anterior leaflet of the mitral valve as a patch. Alternatively, it is easy to use pericardium as a patch[23 24] and thus avoid all prosthetic material in the reconstruction of the right ventricular outflow tract.

In our series the major cause of recurrent right ventricular outflow tract obstruction was the development of a proliferative neointimal peel in the Dacron conduit. It seems that the development of neointimal peel is inevitable.[11–13 25] There is evidence that the valve itself may exacerbate peel formation.[13]

A fibrous peel was present in all of the 10 children undergoing reoperation, and in varying degrees it obstructed the conduit on both sides of the Björk-Shiley valve. Small amounts of thrombus, both old and new, were also found in the Björk-Shiley valve mechanism itself. In one case the valve was partly obstructed and fixed in an open regurgitant position by peel prolapse and thrombus. In another case the largest peel was found distal (Fig. 2) to the valve and the proximal peel was thinner and adhered to the Dacron graft.

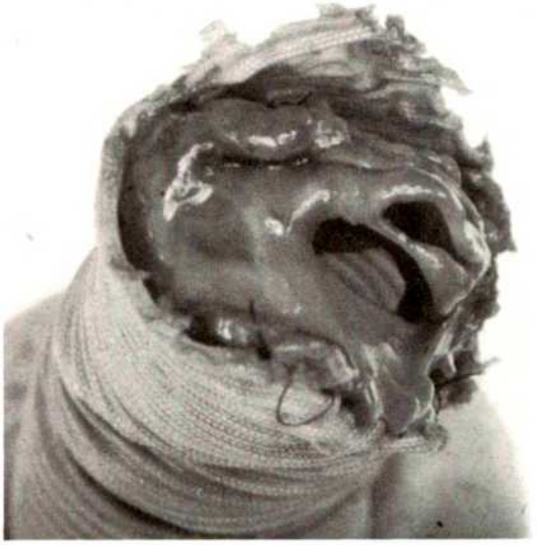

Fig. 2 *Thick fenestrated and friable neointimal peel in distal conduit.*

The reoperation rate is high (52% of survivors), and compares unfavourably with reported reoperation rates of 0·8%–30% for conduit stenosis in the presence of biological valves.[17 25] Development of this neointimal peel is slow. The time of reoperation varies between four and 10 years (mean five years) and in our experience most patients requiring reoperation present in the fifth postoperative year.

The conduit with Björk-Shiley valve has not performed well in the right ventricular outflow tract because of the inevitable development of neointimal proliferative conduit stenosis with subsequent valve malfunction. Our experience suggests that mechanical valves should be avoided in right ventricular outflow tract reconstruction.

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*Br Heart J* 1986; 55: 376–80

# Accessory mitral valve tissue causing left ventricular outflow tract obstruction

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SUMMARY Although left ventricular outflow tract obstruction is commonly associated with congenitally corrected transposition of the great vessels, this obstruction is seldom caused by accessory mitral valve tissue. Three cases in which accessory mitral valve tissue caused left ventricular outflow tract obstruction in children are described. Two had congenitally corrected transposition and one had normally connected great vessels. The accessory leaflet tissue, which was identified by echocardiography and angiography, was attached by chordae tendineae to normally sited papillary muscles and herniated into the left ventricular outflow tract during systole.

Operation was successful in these patients. The accessory valve tissue was excised via an arteriotomy in the great vessel that arose from the left ventricle. The obstructive tissue was excised close to its peripheral attachments in the outflow tract and its chordae tendineae were divided. Resection was performed without injury to the abnormally placed conduction system or to the normal valve structures.

In congenitally corrected transposition the outflow of the right sided morphologically left ventricle to the pulmonary artery is obstructed in 33% to 50% of cases. This obstruction may be at the level of the pulmonary valve but is more commonly subvalvar. Also in about 80% of all cases of corrected transposition with pulmonary stenosis a ventricular septal defect is present, and in a third of these cases there are morphological tricuspid valve anomalies.[1-3]

We report three patients with accessory mitral valve tissue which caused left ventricular outflow tract obstruction in two children with congenitally corrected transposition and in one child with normally connected great vessels.

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Accepted for publication 26 November 1985

Table *Accessory mitral valve tissue causing left ventricular outflow tract obstruction*

| *Patient* | *Sex* | *Age (yr)* | *Pathology* | *Pressure gradient in the outflow tract of the morphological left ventricle (mm Hg)* | *Operation* | *Result* |
|---|---|---|---|---|---|---|
| 1 | M | 8 | Congenitally corrected transposition, pulmonary stenosis, accessory MV tissue | 112 | Pulmonary valvotomy and resection of accessory MV tissue via MPA | Well, residual gradient of 40 mm Hg |
| 2 | M | 15 | Congenitally corrected transposition, accessory MV tissue | 103 | Resection of accessory MV tissue | Well |
| 3 | F | 7 | Accessory MV tissue, muscular subaortic stenosis | 80 | Resection accessory MV tissue, limited myomectomy | Re-do myomectomy for SAS, two years after operation |

MV, mitral valve; MPA, main pulmonary artery, SAS, subaortic stenosis

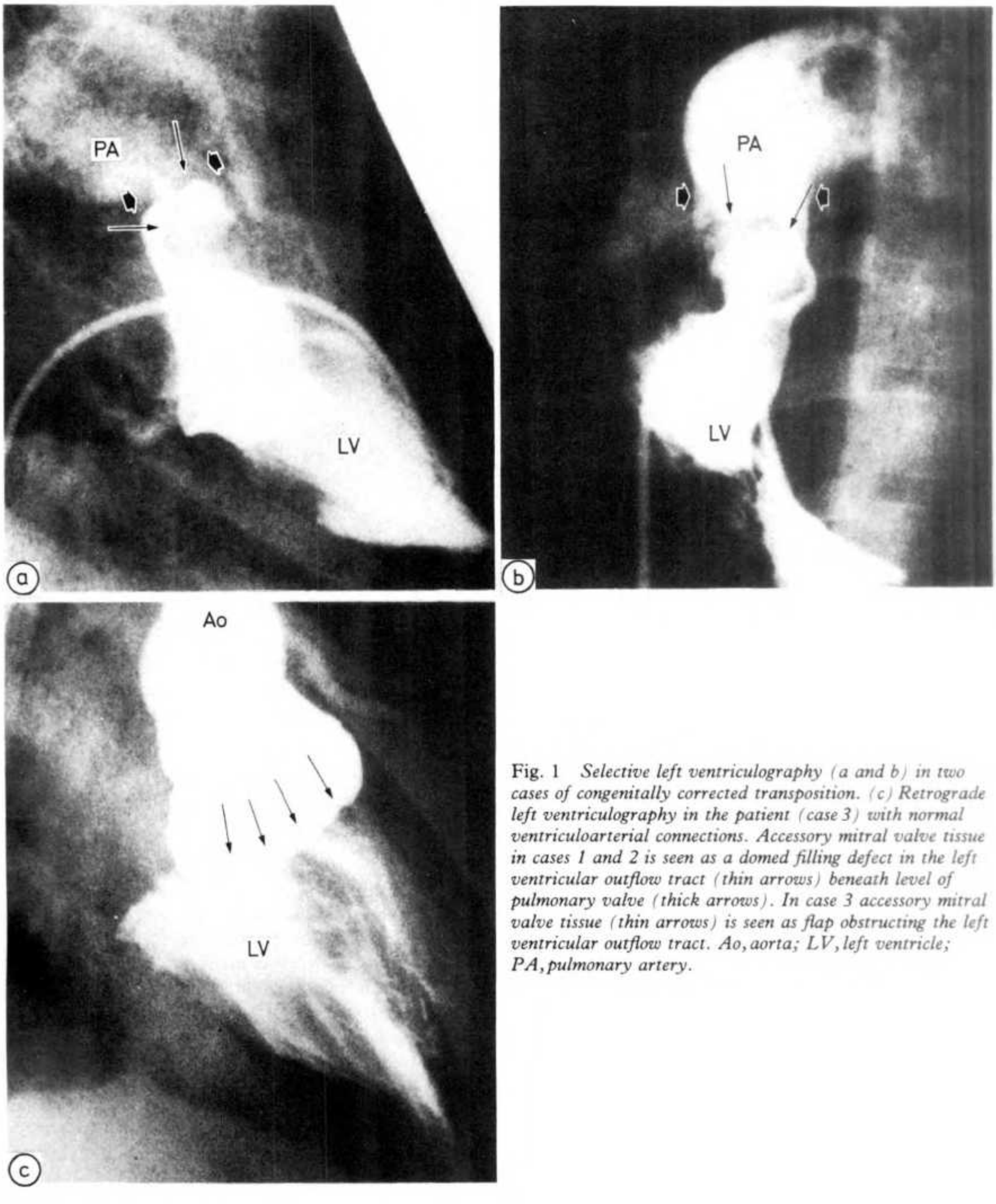

Fig. 1 *Selective left ventriculography (a and b) in two cases of congenitally corrected transposition. (c) Retrograde left ventriculography in the patient (case 3) with normal ventriculoarterial connections. Accessory mitral valve tissue in cases 1 and 2 is seen as a domed filling defect in the left ventricular outflow tract (thin arrows) beneath level of pulmonary valve (thick arrows). In case 3 accessory mitral valve tissue (thin arrows) is seen as flap obstructing the left ventricular outflow tract. Ao, aorta; LV, left ventricle; PA, pulmonary artery.*

## Patients and methods

Between 1980 and 1984 three children (aged 6–15 years) presented at this hospital for investigation of left ventricular outflow tract obstruction (Table). Two children (cases 2 and 3) had dyspnoeic grade I New York Heart Association class heart disease. The other child was symptom free but presented with a murmur. Two children (cases 1 and 2) had congenitally corrected transposition; one of them (case 2) also had a ventricular septal defect which had closed spontaneously before operation. The remaining child (case 3) had normally connected great vessels but also had some muscular subaortic stenosis. All patients had left ventricular outflow tract gradients >80 mm Hg (range 80–112 mm Hg).

All patients had selective ventriculography and cross sectional echocardiography.

## Results

### VENTRICULOGRAPHY

Selective ventriculography demonstrated the accessory mitral valve tissue as dome shaped filling defects in the left ventricular outflow tract during systole. These defects were difficult to visualise during diastole when the valve tissue collapsed back into the body of the ventricle (Fig. 1).

### ECHOCARDIOGRAPHY

Cross sectional echocardiography was performed in all three children. Both short axis and long axis views demonstrated a mobile filling defect which moved rapidly into the left ventricular outflow tract during systole and then prolapsed back into the body of the ventricle during diastole (Fig. 2a and b).

### OPERATION

Cardiopulmonary bypass with moderate hypothermia (25°C) and cold potassium cardioplegia was used routinely. After transverse pulmonary arteriotomy (cases 1 and 2), the valvar and subvalvar region was examined. Very gentle retraction in the region of the subvalvar area allowed the accessory mitral tissue to be seen and excised; it also avoided damaging the attenuated conduction system running anterolaterally round the ventricular attachment of the pulmonary valve leaflets.[4] The obstructive tissue was easily grasped and excised around its peripheral attachments in the outflow tract, and its chordae tendineae were divided close to the papillary muscle.

The child with normal ventriculoarterial connections and subaortic muscular stenosis (case 3) had an oblique aortotomy, excision of the accessory mitral valve tissue, and a limited septal myotomy as well. All patients were weaned from bypass in sinus rhythm. There have been no instances of late heart block during a follow up of from two to five years.

### OPERATIVE PATHOLOGY

The accessory mitral valve tissue (Fig. 3) was excised in each case. Typically (cases 1 and 2) the tissue took the form of an accessory dome shaped leaflet attached partly to the right rim of the outflow tract. Its free edge was supported by one prominent chorda and two or three minor chordae. The major chorda was attached to the apex of a large papillary muscle which it shared with normal chordae of the mitral valve. During systole the accessory leaflet ballooned out into the left ventricular outflow tract and caused severe obstruction. The pulmonary valve was slightly stenosed in case 1. In case 3, the patient with the normal ventriculoarterial connection, the accessory leaflet was attached around the leftward part of the anterior mitral valve leaflet and ran on to the septum for about a third of the circumference of the outflow tract. There were also some short chordae along the free edge attaching the leaflet to the wall of the outflow tract.

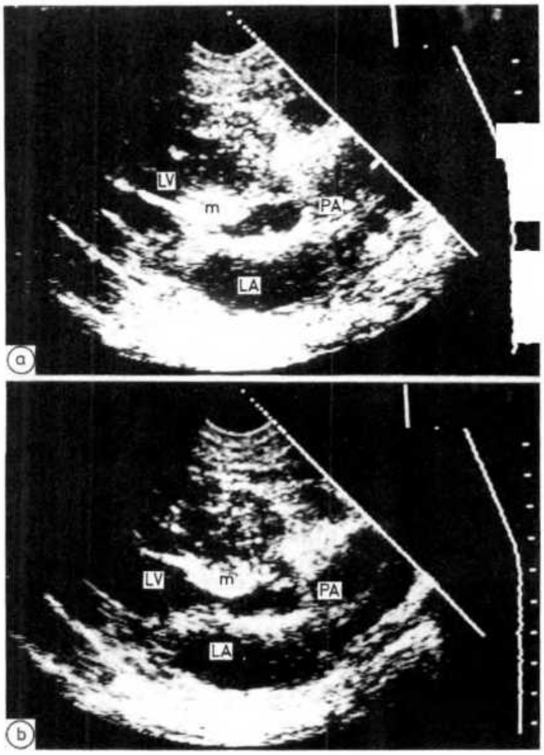

Fig. 2 *Cross sectional echocardiography in long axis view in case 1 with congenitally corrected transposition. Accessory mitral valve (m) seen moving into left ventricular outflow tract during systole (a) and prolapsing back into the left ventricle during diastole (b). PA, pulmonary artery; LA, left atrium; LV, morphological left ventricle.*

## Discussion

Anomalies of the mitral valve causing simple left ventricular outflow tract obstruction are uncommon,

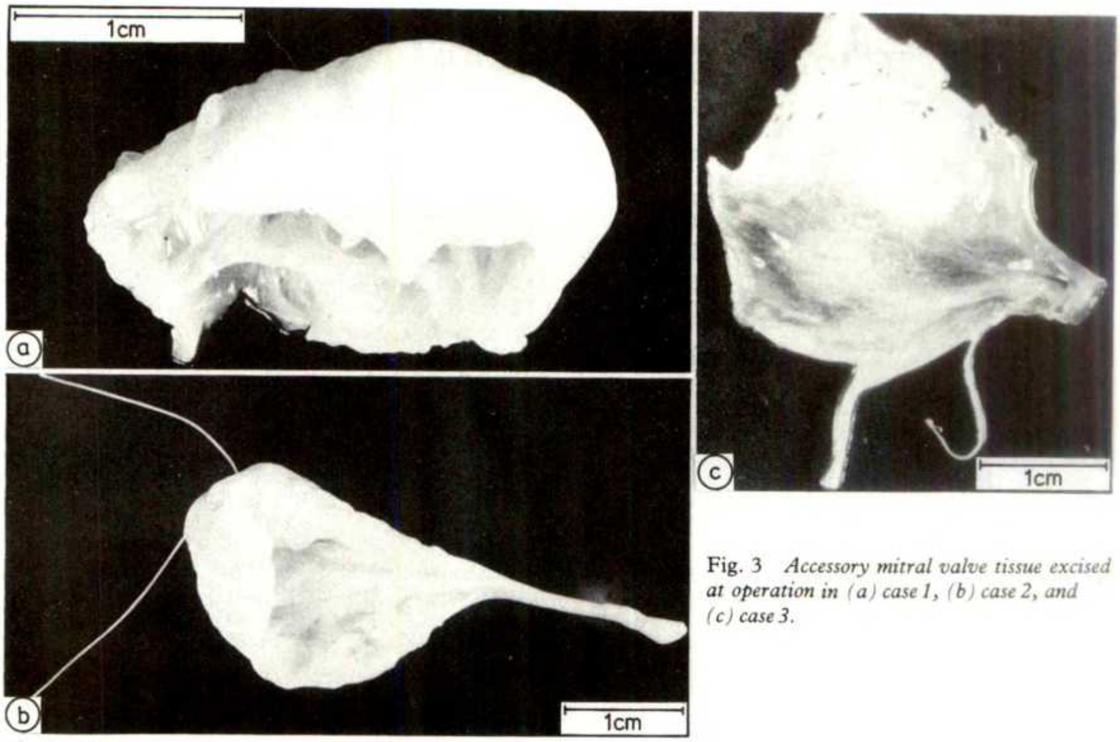

Fig. 3 *Accessory mitral valve tissue excised at operation in (a) case 1, (b) case 2, and (c) case 3.*

but atrioventricular valve anomalies are frequently (20%) seen in cases of congenitally corrected transposition.[1 2 5] These are usually "aneurysmal" dilatations of fibrous tissue in the region of the left ventricular outflow tract. This tissue was described initially as originating from the morphological mitral valve by Tonnies in 1884.[6] Levy *et al* in 1963 described three necropsy specimens from patients with congenitally corrected transposition in which two had "umbrella" like formations of accessory valvar tissue protruding into the subpulmonary area.[7] This tissue was attached by chordae-like strands to pulmonary and atrioventricular tissue and to the superior edges of the ventricular septal defect. The accessory tissue obstructed both the ventricular septal defect and the subpulmonary region. Another patient, without ventricular septal defect, had valve tissue, without chordae, attached to the ventricular aspect of the atrioventricular valve.

Aneurysmal tissue tags arise more commonly from bulging of the interventricular septum (membranous component)[8] or from redundant tricuspid valve tissue herniating through a ventricular septal defect[9-14] and less commonly from the pulmonary valve itself.

Abnormalities of the mitral valve causing left ventricular outflow tract obstruction are less common.[14] MacLean *et al* reported subaortic stenosis caused by accessory tissue on the mitral valve which formed two cup-shaped "diverticula" on the ventricular surface of the anterior leaflet of a patient presenting with dextrocardia.[15] Deal *et al* reported another case in which there were slit-like fenestrations of an aneurysmal bulging accessory leaflet which were thought to represent an attempt at reduplication of the mitral valve.[16] Both sets of workers noted that it was difficult to identify the tissue at operation. The diagnosis was not made before operation because left heart catheterisation had not been performed. Subaortic stenosis has also been reported with abnormal attachment of the anterior leaflet of the mitral valve, either directly to the interventricular septum or via abnormal chordae to the septum.[17 18]

The three children we have described in this paper all had accessory mitral valve leaflet tissue that almost duplicated the anterior leaflet. This tissue was continuous with the left ventricular outflow tract valve annulus and was attached by its own chordae to otherwise normally sited papillary muscles.

Successful operation was relatively simple. We approached the accessory tissue via the pulmonary artery (or aorta) and took care not to damage the conduction system. The accessory leaflet tissue was excised close to its attachment to the base of the outflow tract valve and redundant chordae were divided near their papillary muscle insertion.

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*Br Heart J* 1986; 55: 381–4

# Doppler ultrasound in the estimation of the severity of pulmonary infundibular stenosis in infants and children

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SUMMARY Pressure gradients estimated by Doppler echocardiography were compared with values obtained at cardiac catheterisation in 31 children (aged seven days to 16 years, mean 2 years 7 months) with pulmonary infundibular stenosis including 16 with tetralogy of Fallot. Various parasternal and subcostal positions were explored to obtain the maximum velocity of blood flow and the obstructive gradient was calculated from the modified Bernoulli formula. The gradient across the obstruction could be measured directly at the time of catheterisation in only 21 patients. The correlation coefficient for the Doppler and total measured gradients was $r = 0{\cdot}90$ for catheter entry and $r = 0{\cdot}77$ for catheter withdrawal. Doppler ultrasound, by measuring the total gradient from the right ventricle to the pulmonary artery, provides a non-invasive assessment of the severity of pulmonary stenosis, and in those with infundibular obstruction allowance need not be made for possible energy losses caused by the elongated obstruction or the presence of narrowing at more than one level.

The development of Doppler echocardiography as a technique to provide a non-invasive assessment of the pressure gradient in obstructive cardiac lesions[1 2] has been an important advance in the management of congenital heart disease. Several studies attest to its accuracy in pulmonary valve stenosis[3–10] but Doppler measurements have been compared with measured gradients in only two patients with infundibular stenosis.[5] With Doppler echocardiography the pressure gradient is calculated by measuring the maximum velocity of blood flow across the obstruction and applying the modified Bernoulli equation. This simplified equation has generally been applied where there is a discrete obstruction and ignores energy losses due to friction. There may therefore be potential errors in applying the formula to patients with infundibular pulmonary stenosis where the obstruction can be elongated or can occur at more than one level. We therefore considered it important to review our experience and assess the validity of the modified Bernoulli formula in the measurement of pressure gradient in patients with infundibular pulmonary stenosis.

## Patients and methods

We studied 31 infants and children aged seven days to 16 years (mean 2 years 7 months) with infundibular pulmonary stenosis proved by cardiac catheterisation and angiocardiography. Fifteen were considered to have infundibular and possible valve stenosis with a ventricular septal defect and 16 had tetralogy of Fallot. One had undergone repair of tetralogy of Fallot, and although the angiocardiogram suggested some residual infundibular narrowing the pressure gradient was small (15 mm Hg). At catheterisation pressures were measured through a fluid filled catheter and the gradient across the obstruction was recorded as the peak to peak difference not only on catheter withdrawal but also as the catheter was initially advanced into the right ventricle and pulmonary artery. Such measurements were possible in only 21 patients (11 had ventricular septal defect with infundibular pulmonary stenosis

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Accepted for publication 13 January 1986

and 10 had tetralogy of Fallot); in the others no attempt was made to pass the catheter into the pulmonary artery because of the severity of the obstruction or the attempt was abandoned when arrhythmia developed. The pressure recordings were reviewed and the measurement of the peak to peak difference was made independently by an observer who was unaware of the Doppler findings.

Where possible an effort was made to obtain a Doppler recording before the child was sedated for catheterisation. In several younger ones this was not possible since even minor movements of the child made it impossible to obtain the exact angulation of the probe or to maintain it for sufficiently long to record an adequate Doppler signal. With the child quiet, sedated, or asleep, satisfactory recordings were obtained, however, from all patients. Of the 21 in whom the gradient was measured 11 underwent the Doppler study while sedated for catheterisation, three within 24 hours of catheterisation, and the other seven on admission for subsequent operation. In one patient the Doppler study was performed with simultaneous measurement of pressure in the pulmonary artery and right ventricle by two catheters. In the other patients the Doppler study was not carried out with a catheter in the pulmonary artery because of possible complications related to infundibular obstruction.

The Doppler equipment consisted of a multifrequency continuous and pulsed wave unit (Alfred, Vingmed) which was used in the continuous mode with a 2 MHz transducer, the signal being monitored on a spectrum analyser (Doptek) fitted with a movable marker line. As the examination proceeded the line was, as necessary, moved to the average of the highest velocities obtained; this permitted easy comparison of the received frequency shift with the previous maximum and ensured that the highest value for the whole investigation was obtained. A cross sectional echocardiogram was initially obtained with an ATL sector scanner, which confirmed the diagnosis and, by demonstrating the intracardiac anatomy, suggested positions from which the Doppler beam might most accurately be aligned along the right ventricular outflow. Although this position was initially used, other subcostal, precordial, suprasternal, and supraclavicular sites were explored to obtain the signal with the maximum Doppler shift. Care was taken to obtain reproducible signals showing as far as possible many high velocity signals with a clear and complete envelope. At the end of the examination the level of the marker line on the spectrum analyser indicating the maximum frequency shift (in KHz) for the whole examination was used to calculate the maximum velocity (V) in metres per second and the pressure gradient (P) in mm Hg from the modified Bernoulli formula, $P = 4V^2$. The estimated and measured pressure gradients were compared in the 21 patients in whom both were measured.

## Results

Pressure gradients measured at catheterisation from separate right ventricular and pulmonary arterial recordings as the catheter was advanced were compared with those obtained on catheter withdrawal. There was considerable variation with a correlation coefficient of 0·87 ($y = 0{\cdot}92x + 6{\cdot}6$). The difference was generally related to variation in the right ventricular pressure measurement on catheter withdrawal caused by extrasystoles which altered the right ventricular pressure values making it difficult for the independent observer to assess a true right ventricular systolic pressure.

Satisfactory Doppler recordings were obtained

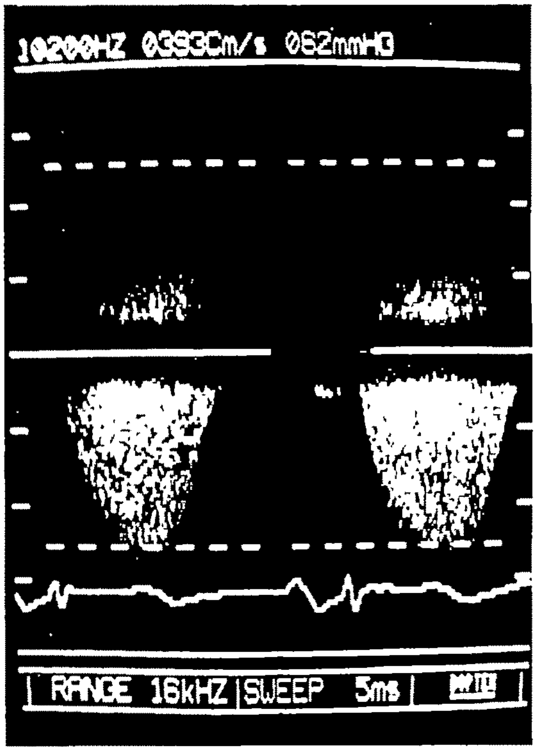

Fig. 1 *Recording of the Doppler signal from the spectrum analyser from a patient with infundibular pulmonary stenosis. The signal which is systolic in timing shows a negative deflection indicating flow away from the transducer The broken lines are the markers which give a maximum frequency shift of 10 200 Kz representing a velocity of* $3{\cdot}93\ ms^{-1}$ *and a gradient of 62 mm Hg.*

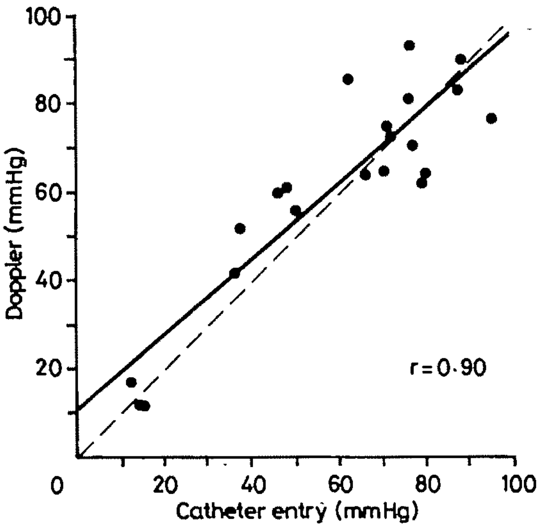

Fig. 2 *Comparison of the pressure gradients measured at catheter entry and estimated by Doppler signal. The linear regression line has a gradient of 0·85 (y=0 85x+10 70).*

from all patients (Fig. 1). Maximum blood flow velocities were obtained almost equally frequently from subcostal and parasternal positions as flow away from the transducer. In one patient a satisfactory signal could be obtained from a parasternal position only from the second left intercostal space as flow towards the transducer. Comparison of the maximum Doppler gradient with that measured on catheter withdrawal showed a correlation coefficient of 0·77 (y=0·77x+17·05); for catheter entry a correlation coefficient of 0·90 was obtained (Fig. 2). Since the Doppler study was performed with the child in a relatively undisturbed state and not at catheter withdrawal, the most appropriate comparison is that of Doppler with pressure gradient at entry.

In the patient in whom two catheters were used the peak to peak gradient was 62 mm Hg on entry, 70 mm Hg on withdrawal, and 80 mm Hg with two catheters (instantaneous maximum 85 mm Hg) and the simultaneous Doppler value was 86 mm Hg.

## Discussion

The ability of Doppler ultrasound to provide an assessment of the pressure gradient in patients with pulmonary valve stenosis has been confirmed by several groups of investigators. Studies have shown a good correlation between the gradient measured at catheterisation and that calculated from Doppler ultrasound, both continuous and pulsed, in patients with discrete pulmonary valve stenosis.[3-10] Reports on Doppler ultrasound in infundibular stenosis are scanty[3 5] and measured pressures were given for only two patients.[5]

The Bernoulli formula relates the pressure gradient to the kinetic energy content of a fluid before and after an obstruction and this will not change whether the obstruction is discrete or elongated. Application of the modified formula $P=4V^2$, however, assumes that there is no energy loss due to viscous friction which may become more important as the length of the obstruction increases. It has not yet been confirmed that this formula can be applied where the narrowed segment is elongated or curved, or when obstruction occurs at more than one level, as can happen in patients with tetralogy of Fallot or with infundibular and valve stenosis. Thus we considered it appropriate to examine whether under these circumstances the simple modified Bernoulli formula remained valid or whether allowance needed to be made for frictional losses or obstruction at more than one level.

One of the major difficulties in any study of Doppler assessment of gradient is accurate measurement of the method against which it is to be compared. The correlation is better when the Doppler measurement is made at catheterisation rather than at another time[8 11] and is further improved by the simultaneous measurement of the gradient with two catheters, one proximal and the other distal to the obstruction. Even then Doppler gives the maximum instantaneous pressure drop and not the peak to peak difference.[8 9] This may be important in aortic stenosis[9 12] but, because of the low pulmonary artery pressure, it is of less importance in pulmonary stenosis and for practical clinical purposes can be ignored. Although Doppler echocardiography was performed at the time of catheterisation in 11 patients in this study, in all but one patient it was considered inappropriate to do so at catheter withdrawal or with two catheters because of possible complications related to leaving the catheter through the narrowed infundibulum while the Doppler investigation was undertaken. In the patient in whom two catheters were used the results confirmed that correlation was improved when the Doppler result was compared with the result measured by this technique.

We found that the apparent variation in pressure gradient with time when entry and withdrawal pressures were compared with Doppler was associated with difficulties in obtaining an accurate right ventricular pressure after withdrawal in some patients in whom extrasystoles occurred. Thus it seems more appropriate to compare the Doppler measurement performed when the child was undisturbed with those obtained as the catheter entered the right ventricle (and when there were no extrasystoles) and when a stable pulmonary artery pressure was obtained. This does provide the better correlation and suggests that the simple modified Bernoulli formula is as applicable in cases with infundibular stenosis or infundibular and valve stenosis as in those with discrete obstruction. In keeping with previously reported findings,[3 5] however, Doppler has not been shown to give any information on the level of obstruction or the relative contribution of infundibular or valvar narrowing to the total gradient. Using pulsed wave Doppler Hatle and Angelsen have been able to predict the presence of infundibular stenosis,[3] but the equipment that they used could not measure the high velocities occurring when obstruction was clinically important. Pulsed wave Doppler with a lower transducer frequency or higher pulse repetition frequency can measure higher velocities from areas near to the transducer but neither pulsed nor continuous Doppler has yet been shown to be able to determine the relative importance of infundibular and valvar obstruction in these cases.

Doppler ultrasound has been able to provide an assessment of the pressure gradient when this could not be measured because of the potential hazard of passing a catheter through a severely narrowed outflow tract. In some of these patients clinical and echocardiographic assessment indicate the need for angiocardiography or operation but there are others in whom the degree of infundibular stenosis changes with time and a non-invasive technique for performing serial measurement of the obstruction will be important. Although Doppler ultrasound cannot yet determine the relative importance of valve or subvalve stenosis the decision on the need for operation is based on the total gradient and anatomical knowledge (echocardiographic or angiocardiographic) of the right ventricular outflow tract is much more useful to the surgeon than physiological information about the relative contributions of the infundibulum and valve to the total obstruction.

Those who are unfamiliar with the principles of the Bernoulli formula may be surprised that it provides accurate values in patients, such as those with tetralogy of Fallot, in whom there can be considerable variation with time in the severity of the infundibular stenosis with major changes in the volume of blood flowing through the right ventricular outflow. In these patients, however, the pulmonary artery pressure is relatively constant and the right ventricular pressure, which is at systemic level will show only relatively small changes; and although variation in flow can occur the pressure gradient will change little. The Bernoulli formula measures the pressure drop that is related to the increase in velocity and is independent of size of orifice and can therefore provide an accurate prediction of the gradient.

The results of this study are in accord with those previously reported in patients with discrete obstruction and the two with infundibular stenosis. They indicate that allowance need not be made for energy losses due to friction, and that the simple modified Bernoulli formula can provide an accurate assessment of the severity of pulmonary stenosis whether it occurs at valve or infundibular level or at both.

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# Effect of long term oxygen treatment at home in children with pulmonary vascular disease

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SUMMARY Inhalation of 100% oxygen by nine children with pulmonary vascular disease increased pulmonary blood flow measured at cardiac catheterisation; there was no significant change in pulmonary artery pressure. Fifteen children with pulmonary vascular disease that was severe enough to preclude corrective cardiac operation were studied to determine the effect of long term oxygen treatment on pulmonary vascular disease. Nine received long term domiciliary oxygen for a minimum of twelve hours a day for up to five years. Though the untreated group closely resembled the treated group their survival was significantly less good. All nine treated children are alive whereas five of the six children who did not receive oxygen have died.

Pulmonary vascular resistance is often raised in children with congenital heart defects and is always raised in those with primary pulmonary hypertension, which is a rare condition. In many such children the pulmonary vascular resistance can be reduced by a pulmonary vasodilator such as oxygen, tolazoline, or epoprostenol (prostacyclin). But when the resistance remains $>8\,mm\,Hg.l^{-1}.min.m^2$ ($640\,dyn.s.cm^{-5}.m^2$) during optimal ventilation with 100% oxygen, surgical repair of the cardiac defect is associated with an unacceptably high risk of perioperative death or may lead to accelerated deterioration in the pulmonary vascular bed.[1 2] These children have hypertensive pulmonary vascular disease, and pathological changes in the pulmonary arterioles are invariably found at biopsy.[3 4] They also have reduced exercise tolerance and a poor prognosis. At present there is no effective and accepted treatment.

Measurements during cardiac catheterisation (both published[5] and our own which are described below) show that in all cases that were studied inhalation of 100% oxygen produced some fall in pulmonary vascular resistance compared with that in air. This shows that there is an additional but reversible element of vasoconstriction contributing to the raised pulmonary vascular resistance and superimposed on the permanent (irreversible) destructive or obliterative changes in the vascular bed.[4]

Experimental use of crotalaria alkaloids in rats shows that they cause intense pulmonary vasoconstriction followed by obliteration with fibrinoid necrosis.[6] Wagenvoort and Wagenvoort infer from this, and from the charactertistic siting of the obliterative lesions in patients, that fibrinoid necrosis may be the result of intense vasospasm both in children with primary pulmonary hypertension and in those with intracardiac shunts.[4]

The response to oxygen and the relation of vasospasm to tissue damage suggested that prolonged oxygen treatment might benefit children with persistently raised pulmonary vascular resistance. The hypothesis on which the trial was based is that the local pharmacological effect of oxygen in relieving vasospasm might prevent or delay a cycle of increasing damage in which superimposed (reversible) vasoconstriction would accelerate destructive changes. The trial was prompted by the pronounced improvement noted in two girls with pulmonary vascular disease and cyanosis who had been using domiciliary oxygen for two or three years when the trial began. They continue to use it but are not included in the trial.

By analogy with studies at altitude[7] and the trials of oxygen treatment in patients with chronic

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Accepted for publication 10 December 1985

Table 1 *Data on individual patients*

| *Diagnosis* | *Age at catheterisation (yr)* | $\overline{PAP}$ *(mm Hg)* | | *PVR (mm Hg.l$^{-1}$.min m$^2$)* | | *On entry into trial* | | | *Symptom score* |
|---|---|---|---|---|---|---|---|---|---|
| | | *Air* | *Oxygen* | *Air* | *Oxygen* | *Age 1980* | *Hb (g/dl)* | *$O_2$ saturation (%)* | |
| Untreated group: | | | | | | | | | |
| 1 Primary PHT | 5 | 70 | — | — | — | 7·5 | 13·8 | 81 | 19 |
| 2 A-P window* | 11 | 63 | 61 | 33 | 28 | 13·7 | 14·3 | 95 | 33 |
| 3 VSD | 8 | 85 | 80 | 23 | 19 | 11·0 | 15·1 | 85 | 28 |
| 4 VSD | 9 | 85 | 85 | 36 | 25 | 9·5 | 15·9 | 68 | 30 |
| 5 UVH | 4 | 47 | 42 | 12·7 | 8 | 4·6 | 15·4 | 83 | 17 |
| 6 UVH | 2 | — | 59 | — | 16 | 7·0 | 19·3 | 74 | 18 |
| Mean | 6·5 | 70 | 65 | 26 | 19 | 8·9 | 15·6 | 81 | 24 |
| SEM | — | 6·4 | 6·9 | 4·6 | 3·1 | 1·2 | 0·7 | 3·5 | 2·5 |
| Treated group | | | | | | | | | |
| 7 Primary PHT | 13 | 39 | 50 | 15 | 8·4 | 14·9 | 13·9 | 97 | 24 |
| 8 DA† | 6 | 74 | — | 12 | — | 5·5 | 14·2 | 97 | 32 |
| 9 VSD | 0·8 | 75 | 75 | — | — | 5·0 | 15·3 | 86 | 18 |
| 10 VSD | 7 | 58 | 58 | 17 | 12·5 | 9·0 | 18·2 | 89 | 25 |
| 11 VSD | 0·8 | — | 70 | — | 39 | 10·2 | 20·5 | 73 | 21 |
| 12 VSD + DA | 8 | — | 70 | — | 6·4 | 9·0 | 17·7 | 83 | 21 |
| 13 Corr TGA | 0·5 | 120 | — | 28 | — | 7·6 | 15·0 | 93 | 22 |
| 14 AV canal | 4 | 60 | 70 | 17·1 | 11·4 | 5·1 | 14·5 | 84 | 17 |
| 15 AV canal | 3 | 82 | 76 | 25 | 9·6 | 7·0 | 18·3 | 76 | 19 |
| Mean | 4·8 | 73 | 67 | 19 | 14·6 | 8·1 | 16·4 | 86 | 22 |
| SEM | — | 8·8 | 3·3 | 2·3 | 4·5 | 1·0 | 0·7 | 2·7 | 1·5 |

*Aortopulmonary window closed age 9 years. †Ductus arteriosus closed age 3 years
*Conversion factor*: traditional units to SI units—1 mm Hg.l$^{-1}$.min $\simeq$ 80 dyn.s.cm$^{-5}$.
PHT, pulmonary hypertension; A-P window, aortopulmonary window; VSD, ventricular septal defect; UVH, univentricular heart; DA, ductus arteriosus; Corr TGA, physiologically corrected transposition of the great arteries, AV canal, atrioventricular canal, $\overline{PAP}$, mean pulmonary artery pressure, PVR, pulmonary vascular resistance, Hb, haemoglobin concentration

bronchitis[8 9] we expected that treatment for a minimum of 12–15 hours a day for at least two years would be needed to show a beneficial effect. For this reason the design of the trial was based on two parallel groups without cross over or placebo.

## Patients and methods

Patients considered for the trial were of school age (four to 18 years) and had primary pulmonary hypertension or pulmonary vascular disease secondary to cardiac defects that was severe enough to preclude surgery or had persisted after operation. Patients with important parenchymal lung disease were not included.

Fifteen children entered the trial during 1980 and 1981. The child's paediatrician or cardiologist allocated their patient to the treatment group after full discussion with the parents. The demands of the treatment and the small numbers studied precluded random allocation or the individual matching of controls.

Table 1 shows the underlying diagnosis, mean pulmonary artery pressure, and pulmonary vascular resistance measured during cardiac catheterisation. The treatment and non-treatment groups both contained one child with primary pulmonary hypertension and one child with pulmonary hypertension persisting after operation. Mean age at entry to the trial was similar in the two groups.

The mean pulmonary artery pressures, which where possible were measured both in air and oxygen, are similar in the two groups. Pulmonary vascular resistance was not measured in all patients. Mean pulmonary vascular resistance both in air and oxygen (Table 1) was higher in the untreated group, but these differences did not achieve statistical significance (unpaired *t* test, $p > 0·1$ for both).

At every visit the parents answered two questionnaires designed to assess the child's disability. The first (Table 2) assessed exercise tolerance and the second (Table 3) the extent of troublesome symptoms. A high score suggests subjective well-being.

Table 1 indicates the condition of the children at entry into the trial at the beginning of 1980 when haemoglobin, oxygen saturation, and symptom scores were measured. There were no statistically signficant differences between the two groups.

### SELECTION OF PATIENTS FOR TREATMENT

At the beginning of the trial all the parents knew that surgical correction of their child's disease was impossible and that he or she had a limited life expectancy. The rationale for oxygen treatment was explained and we made it clear that its benefits were unproven.

The parents of the children in the treated group

Table 2 *A questionnaire for parents. A scoring system for the assessment of exercise ability*

Please mark the box (or boxes) on each line which best describes your child in the past six months.

Name: Date:

| | *0* | *1* | *2* | *3* | *4* |
|---|---|---|---|---|---|
| School | None | Half time or less | Less than full time or special school | Full time limited sport or none | Full time full sport |
| Walking on the flat | Breathless at rest | Breathless on minimal exertion | 30–50 yards slowly all right | 100–400 yards slowly all right | 2 miles slowly all right |
| Stairs | Never tries | Difficulty with 1 flight | Difficulty with 2 flights—1 all right | 2 flights all right at average speed | Normal |
| Running | Never | Few paces only | 20 yards gently all right | 100 yards jogging all right | Normal speed 100 yards |
| Tiredness | Always | Very quickly tired each day after school | Frequently tired | Sometimes after a long day | Normal |

were prepared to try oxygen treatment and the paediatricians agreed. Three families of children in the untreated group felt that their girls were so well and free of symptoms that they did not want to remind them of their disease. One of these families planned to start oxygen treatment later if the child deteriorated. The parents of one girl who presented with three episodes of syncope saw no other evidence of disability, though the catheter data suggested very severe disease.

The other three children in the non-treatment group were more clearly disabled—one had a pacemaker and his parents felt that oxygen treatment would complicate his life. The other two were being treated by physicians who were less convinced of the benefit of treatment, though one of these two patients was given oxygen treatment in hospital before he died.

Thus though allocation of the children to the two groups was not random the reasons for choosing or not choosing treatment showed no detectable trend.

## METHODS

### *Administration of oxygen*

Oxygen was supplied by oxygen concentrators installed in the child's home with outlets to the bedroom and usually also to the sitting room where the child was able to wear the mask for a few hours before going to bed[10 11] Nasal cannulas were tried initially in all cases, but if these proved unacceptable they were replaced by face masks or tents. We emphasised that the trial required oxygen administration for a minimum of twelve hours a day, preferably fifteen.

Strict monitoring of the use of the machines proved impracticable because of the great geographical spread of patients. But on each visit both the parents and the child were questioned carefully about the number of hours for which oxygen was used, the frequency of equipment breakdowns, and nights missed because of holidays.

### *Assessment during cardiac catheterisation*

Before inclusion in the trial nine of the fifteen children were studied while breathing air and oxygen during cardiac catheterisation by means of respiratory mass spectrometry.[5 12] The patients were anaesthetised, intubated with a leak-free endotracheal tube, and ventilated optimally with air to maintain a normal and constant arterial $P\text{CO}_2$. Semi-continuous measurements of metabolic gas exchange were made at the same time as pulmonary artery and left atrial pressures were measured, and samples were drawn from the pulmonary artery and pulmonary veins or systemic circulation as appropriate. The total oxygen content of the blood samples was derived from the blood gases and haemoglobin concentration by the tables of Kelman.[13]

The patients were then ventilated with 100% oxygen for at least 10 minutes, and the end tidal and arterial carbon dioxide concentrations were compared to ensure as steady a state as possible. Measurements were repeated, and the cardiac output and pulmonary vascular resistance were calculated by the method described by Davies *et al.*[5]

Table 3 *A questionnaire for parents*

It would be most helpful if you would answer the following questions about your child's health in the last 6 months. Please tick the box in the appropriate column for each question.

Patient's name: Date·

| | *A major problem often occurring*<br>*0* | *Minor or occasionally troublesome*<br>*1* | *Not a problem*<br>*2* |
|---|---|---|---|
| Does he/she have "bad days" of diminished activity? | | | |
| Is he/she worse in cold weather? | | | |
| Does he/she have:<br>Headaches? | | | |
| Nose bleeds? | | | |
| Chest pain? | | | |
| Leg cramps? | | | |
| Coughing blood? | | | |
| Poor appetite? | | | |
| Faints or dizziness? | | | |
| Chest infections? | | | |
| Has he/she changed in the last 6 months? | | | |

Comments·

### *Non-invasive assessment of progress*

Initial diagnosis and a decision about operation depended on the measurements made during catheterisation. But, in view of the risk of cardiac catheterisation in children with advanced pulmonary vascular disease, we thought it proper to restrict serial assessment during treatment to non-invasive methods. These included a subjective score from a questionnaire, clinical assessment, electrocardiography, echocardiography, and an exercise test. The children were reviewed every six to 12 months for up to five years.

## Results

Figure 1 shows the mean pulmonary artery pressures and pulmonary blood flow in the nine children studied in air and oxygen. There was no significant change in pressure on oxygen, but pulmonary blood flow was consistently increased. This is reflected in the reduction of pulmonary vascular resistance when oxygen was breathed, though this did not fall below $8\,\text{mm Hg.l}^{-1}\text{.min.m}^{2}$ ($\simeq 640\,\text{dyn.s.cm}^{-5}\text{.m}^{2}$) in any case.

### *Acceptability of treatment*

Three children have used nasal cannulas throughout their treatment, four prefer a mask, and the others can only use a tent. Because the equipment can be used in both the bedroom and sitting room, the child's freedom is less restricted. In some cases the provision of oxygen concentrators was delayed for up to 10 months.

### *Compliance*

Four of the nine children complied well with oxygen treatment. These families chose never to go away, or only go away with an alternative oxygen source. Breakdowns accounted for a maximum of only a week missed per year. These four patients used oxygen for at least 12 hours per day (commonly 14

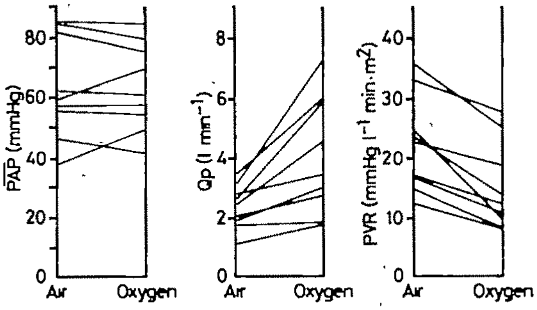

Fig. 1 *Data obtained from measurements made during cardiac catheterisation in nine children with advanced pulmonary vascular disease. The mean pulmonary artery pressure ($\overline{PAP}$), pulmonary blood flow ($\dot{Q}p$), and pulmonary vascular resistance (PVR) are shown first in air, then after optimal ventilation with 100% oxygen for ten minutes. 1 mm Hg.$l^{-1}$ min. ≃ 80 dyn.s.$cm^{-5}$.*

hours). Three of the families reported missing up to three weeks a year due to holidays or breakdowns or both. Otherwise these children appear to have had a steady nightly intake of between 10 and 12 hours. All these seven children seem to tolerate treatment well. But two children have found compliance difficult. After two years of successful treatment one adolescent girl found that treatment was intolerable for a four month period during the summer. For a year a boy, who is now fourteen years old and had tolerated treatment for four years, did not comply with treatment. His parents, feeling that his own perception of the quality of his life was paramount, have agreed to his stopping oxygen treatment.

*Survival*

Figure 2 shows the survival of the children in the two groups. All nine children on oxygen treatment are alive whereas five of the six children not on treatment have died ($\chi^2=9{\cdot}0$, $p<0{\cdot}01$ with Yates's correction). In one child death was thought to be due to a sudden arrhythmia, and another child died after a severe chest infection. Three others became unwell over a period of one to three weeks with increasing cyanosis and exercise intolerance. Only one showed signs of congestive right ventricular failure.

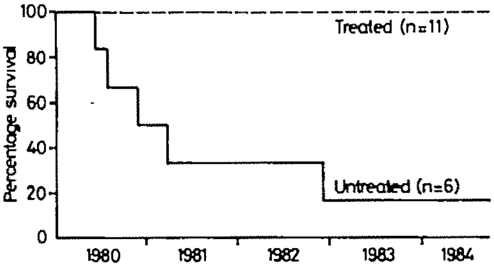

Fig. 2 *A chart showing the survival in the years 1980–84 of children with pulmonary vascular disease in the treated and untreated groups.*

## Discussion

We have shown that there is an additional reversible vasoconstrictive component in most children with severe pulmonary vascular disease. This vasoconstriction can be minimised by optimal ventilation and added oxygen, and is exacerbated by hypoventilation or acidosis. To avoid unwarranted classification of such cases as inoperable, cardiac output must be initially measured under optimal conditions. Figure 1 shows that reliance on changes in pressure alone will lead to important haemodynamic changes being missed. More studies of this type are needed both to define more accurately the risks of operation at different levels of vascular resistance and to determine the correlation between resistance levels and pathological changes in the lungs.

If despite optimal ventilation the pulmonary vascular resistance remains high, operation is contraindicated, and the likely course is one of progressive deterioration. Figure 2 shows that this deterioration can be modified, and survival can be improved.

Deterioration in children with the Eisenmenger complex is associated with increasing right to left shunting which results in a critically low pulmonary blood flow rather than in congestive failure of the right ventricle. There is therefore no reason to suppose that effective pulmonary vasodilatation in this situation causes increased right ventricular work.

This small pilot study shows that long term oxygen treatment at home is well tolerated and improved survival of children with pulmonary vascular disease over a five year period. We believe that the results warrant a larger trial, perhaps at several centres. Recruitment into the trial must be preceded by accurate measurements of pulmonary blood flow under optimal and controlled conditions.

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*Br Heart J* 1986; 55: 391–9

# Afterload reduction: a comparison of captopril and nifedipine in dilated cardiomyopathy

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SUMMARY Nifedipine and captopril are potent vasodilators and may be expected to help left ventricular failure by reducing afterload. Nifedipine (20 mg three times a day) and captopril (50 mg three times a day) were added to an optimal regimen of digitalis and diuretics in a double blind crossover trial in 18 cases of dilated cardiomyopathy. New York Heart Association functional class rating symptoms and exercise tolerance times improved on captopril but not on nifedipine. The reduction in pulmonary capillary wedge pressure and the increase of cardiac output on captopril indicated that the augmented functional capacity may have resulted in part from an improved performance of the left ventricle. Although there were comparable decreases in systemic vascular resistance and presumably in impedence to ejection by the left ventricle on both drugs, the dimensions of the ventricular cavity were found to be reduced by captopril and augmented by nifedipine, and only captopril reduced the afterload (wall stress). In addition, the force-length relation (between left ventricular end systolic stress and end systolic diameter) was shifted to the left of baseline by captopril and to the right by nifedipine, suggesting that muscle contractility was reduced by nifedipine and not by captopril.

These results suggest that nifedipine and captopril have different effects on afterload and contractility and these may account for the different effects of these drugs on the performance of the heart and clinical responses.

Most vasodilators may be beneficial in both hypertension and cardiac decompensation. The angiotensin converting enzyme inhibitor, captopril, is such an example.[1-3] The antihypertensive properties of the calcium channel blocking agents are well established,[4] and nifedipine has been used to reduce ventricular afterload.[5-8]

Treatment of cardiac insufficiency in the advanced stage of dilated cardiomyopathy is still one of the most challenging tasks in clinical cardiology, and the poor prognosis justifies a search for more efficient methods of treatment. Although the combination of captopril with conventional treatment has been of benefit in many series of patients with refractory chronic congestive heart failure,[9-12] these series did not include many cases of dilated cardiomyopathy and the specific response of such patients may have been obscured. Acute pulmonary oedema due to dilated cardiomyopathy can be relieved by nifedipine[5 6] but long term studies are lacking.

For these reasons we have studied the effects of these two agents in dilated cardiomyopathy. We performed a detailed haemodynamic study of the different effects of captopril and nifedipine on blood vessels (in terms of arterial and venous muscle relaxation) and on the myocardium (in terms of changes in heart rate and contractility) in a crossover trial.

## Patients and methods

### PATIENTS

Twenty six patients with chronic congestive heart failure caused by dilated cardiomyopathy of unknown cause were considered to be eligible, but

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Accepted for publication 3 December 1985

Table 1 *Clinical data on 18 patients with dilated cardiomyopathy*

| *Case* | *Age (yr)* | *Sex* | *BSA ($m^2$)* | *ECG* | *Previous drug treatment* |
|---|---|---|---|---|---|
| 1 | 57 | F | 1·26 | SR | Digitalis, frusemide, spironolactone |
| 2 | 54 | M | 1·93 | AF + LBBB | Digitalis, ethacrynic acid |
| 3 | 46 | M | 1·84 | SR | Digitalis, nitrates, hydrochlorothiazide |
| 4 | 61 | M | 1·80 | AF | Digitalis, frusemide |
| 5 | 45 | M | 1·75 | LBBB | Digitalis, nitrates, frusemide |
| 6 | 58 | M | 2·00 | SR+<br>1 degree AVB | Digitalis, ethacrynic acid |
| 7 | 68 | M | 1·57 | SR | Digitalis, frusemide |
| 8 | 58 | M | 2·12 | SR | Digitalis, frusemide |
| 9 | 55 | M | 1·83 | AF | Digitalis, nitrates, frusemide |
| 10 | 49 | M | 1·99 | AF + LBBB | Digitalis, frusemide, spironolactone |
| 11 | 58 | M | 1·82 | SR | Digitalis, nitrates, hydrochlorothiazide |
| 12 | 34 | M | 1·76 | SR | Digitalis, hydrochlorothiazide |
| 13 | 62 | M | 1·88 | SR | Digitalis, frusemide |
| 14 | 38 | F | 1·45 | SR | Digitalis, frusemide |
| 15 | 46 | M | 1·85 | SR | Digitalis, ethacrynic acid |
| 16 | 57 | M | 1·80 | SR +<br>1 degree AVB | Digitalis, frusemide, spironolactone |
| 17 | 52 | F | 1·59 | LBBB | Digitalis, hydrochlorothiazide |
| 18 | 49 | M | 1·82 | SR | Digitalis, frusemide, spironolactone |

BSA, body surface area, ECG, electrocardiogram, SR, sinus rhythm; AF, atrial fibrillation; LBBB, left bundle branch block; AVB, atrioventricular block.

three were lost to follow up, one died, and four were withdrawn because at excessive hypotension on treatment. The remaining 18 patients (Table 1) completed the study. All of them had evident cardiac dysfunction causing dyspnoea at rest and were easily fatigued; six of them also had orthopnoea despite treatment with digitalis and diuretics. Vasodilators (nitrates) were used in four cases and treatment was stopped seven days before the beginning of the study. Eleven patients had had cardiac symptoms for > two years and the other seven had had dyspnoea for at least 10 months. Eleven subjects were in functional class IV (New York Heart Association) and seven were in class III. We excluded those patients who had supine systolic blood pressure < 100 mm Hg, angina pectoris, a history of or electrocardiographic signs of myocardial infarction, and hepatic or renal impairment (serum bilirubin or glutamic oxalacetic transaminase or both more than twice the upper limit of normal, and serum creatinine concentration $\geqslant 2$ mg/dl). Patients were deemed to be eligible for the study if they were capable of exercising for at least three minutes and no more than 12 minutes on a treadmill following the protocol used by the Captopril Multicenter Research Group.[11]

The study protocol was approved by our ethical research committee, and each patient gave informed consent.

### STUDY DESIGN

Patients were admitted to the hospital, and during the first seven days physical examination, 12 lead electrocardiogram, and blood and urine laboratory tests were performed; the dosages of digitalis and diuretics were also adjusted until we judged that an optimal regimen had been achieved. This regimen was kept constant during the trial. At the end of this period a standard 6 ft posteroanterior chest *x* ray was taken to measure the cardiothoracic ratio, and echocardiographic and blood pressure (with random zero sphygmomanometer) measurements were obtained with the patient supine. An exercise test was performed to determine maximum physical capacity. After this, patients were randomly allocated to a treatment group and right heart catheterisation was carried out. Baseline records were obtained 30 min after catheter positioning when patients felt comfortable and heart rate and blood pressure had stabilised. Then nifedipine (20 mg) or captopril (50 mg) was administered and the haemodynamic variables were recorded again every 30 min for the next 120 min. Baseline values were compared with those detected when the fall in blood pressure after the drug was greatest.

Patients continued to take the test drug three times a day as outpatients. Each day patients noted their symptoms in a diary and classified dyspnoea on a scale of 0 to 4 (0 when none occurred, 1+ with more than ordinary activity, 2+ with ordinary physical activity, 3+ dyspnoea at rest, and 4+ orthopnoea). We used the patient's dyspnoea grades to give a serial clinical function classification (from class I to IV).

For two months physical examination, exercise tests, and echocardiographic examination were performed each week. After this, patients were readmitted to hospital and non-invasive and invasive evaluations were repeated 90–120 min after the final dose of the agent. Then patients were switched to the other drug, and continued on it as outpatients. We considered a washout period to be unnecessary in view of the long duration of treatment. The study continued as described earlier. No complications were noticed with repeated haemodynamic monitoring. The cardiothoracic ratio was measured on chest *x* rays obtained at the end of both treatment periods.

Both nifedipine (20 mg) and captopril (50 mg) were given in identical capsules in a double blind randomised fashion in both the short term and long term studies. Capsules containing an inactive preparation were given during the seven day run in period.

### SAFETY

For the first three days of each drug treatment patients remained in hospital and blood pressure and symptoms related to hypotension were monitored. Hypotension with faintness on standing was experienced by three subjects while on nifedipine (one on nifedipine as second drug) and two while on captopril (one on captopril as second drug). In one of these, however, symptomatic hypotension was transient and he was able to continue on captopril; the other four patients could not and they were withdrawn from the trial. No other patients had excessive hypotension or related symptoms during treatment.

### HAEMODYNAMIC ASSESSMENT

Circulatory measurements were obtained in fasting patients who were supine and had not received premedication. For right atrial, pulmonary arterial, and pulmonary capillary wedge pressure measurements and cardiac output determinations, a number 7 triple lumen flow directed thermodilution catheter was inserted percutaneously under local anaesthesia into an antecubital vein and floated under fluoroscopic guidance to the pulmonary artery and, when necessary, to the wedge position. Intra-arterial blood pressure was measured through a Teflon catheter needle introducted into a brachial artery. We used these variables to calculate systemic (SVR) and pulmonary (PAR) arteriolar resistance by the following formulas: $\text{SVR} = \text{AP} - \text{rap} \times 1332/\text{CO}$ and $\text{PAR} = \text{PAP} - \text{WPP} \times 1332/\text{CO}$, where CO is cardiac output (average of three thermodilution determinations), and AP, rap, PAP, and WPP are mean arterial, right atrial, pulmonary arterial and pulmonary capillary wedge pressure respectively. Mean pressures were obtained by electronic damping, and heart rate was derived from the electrocardiogram. All these variables were recorded on a Hewlett-Packard eight channel direct writing recorder (model 7868/A).

### ECHOCARDIOGRAPHIC EVALUATION

Left ventricular end systolic circumferential wall stress was taken as a variable that reflects afterload and was evaluated non-invasively on echocardiograms recorded in triplicate. We used the angiographically validated equation of Grossman and coworkers,[13] as modified by Reichek *et al*[14] to calculate end systolic circumferential wall stress (es CWS):

$$\text{es CWS} = \frac{0{\cdot}334 \times \text{Ps}/\text{LVIDs}}{\text{PWTs}\left(1 + \dfrac{\text{PWTs}}{\text{LVIDs}}\right)}$$

where Ps, LVIDs, and PWTs are systolic cuff arterial pressure, left ventricular minor dimension (cm), and posterior wall thickness (cm) respectively at end systole. Pressure was measured after the patient had been recumbent for 15 min. An independent observer used a random zero sphygmomanometer to take three consecutive measurements with 5 min between measurements. Ultrasound and blood pressure readings were averaged to improve their accuracy; variablity was within 2% for ventricular diameter and within 5% for wall thickness and systolic blood pressure. Two patients with atrial fibrillation, two with left bundle branch block, and two with both were excluded from this analysis because accurate echocardiographic recordings are difficult to obtain in the presence of these disorders.

We used a Hewlett-Packard cross sectional unit (model 77020 A) for echocardiography. The end systolic dimension of the endocardial surface was measured as the shortest distance between the septal and posterior walls during systole. End systolic posterior wall thickness was measured by the leading edge to leading edge method as the point of maximal anterior motion. We analysed the means of three to five consecutive cycles. The end systolic stress–left ventricular end systolic diamater relation was taken as an index of the end systolic force length relation.

### STATISTICAL EVALUATION

All values after treatment were compared with the baseline values by two way analysis of variance. Differences in means were assessed by Student's *t* test.

## Results

Eighteen patients completed the study; all of them had had nifedipine and captopril for eight weeks each in a crossover study (Fig. 1).

Mean exercise tolerance times on captopril were significantly better than baseline values or values on nifedipine (Fig. 2). Nifedipine treatment values were never significantly different from baseline values.

The mean functional class was significantly better while patients were on captopril than at baseline and

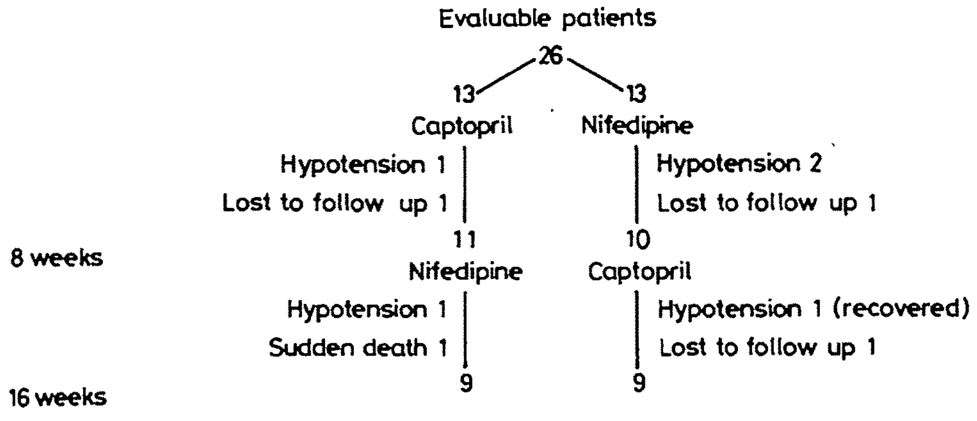

Fig. 1 *Patient treatment.*

on nifedipine treatment (Table 2). Changes in clinical class paralleled the changes in exercise tolerance in all but two patients.

Baseline values for mean arterial pressure averaged 83 mm Hg, and the mean cardiac index for the group was reduced (2·5 l/min/m$^2$). Pulmonary capillary wedge pressure was <20 mm Hg in all except one of the patients, and the mean value (12 mm Hg) was lower than expected given the severity of congestive heart failure. This was probably because patients were on diuretics and on a salt restricted hospital diet. Mean systemic and pulmonary arteriolar resistance was 1480 and 145 dyn s cm$^{-5}$ respectively.

Peak response to oral nifedipine occurred about 1·5 hours after administration. At this time there was a 20% reduction in mean arterial pressure that was mediated through a 29% decrease in systemic vascu-

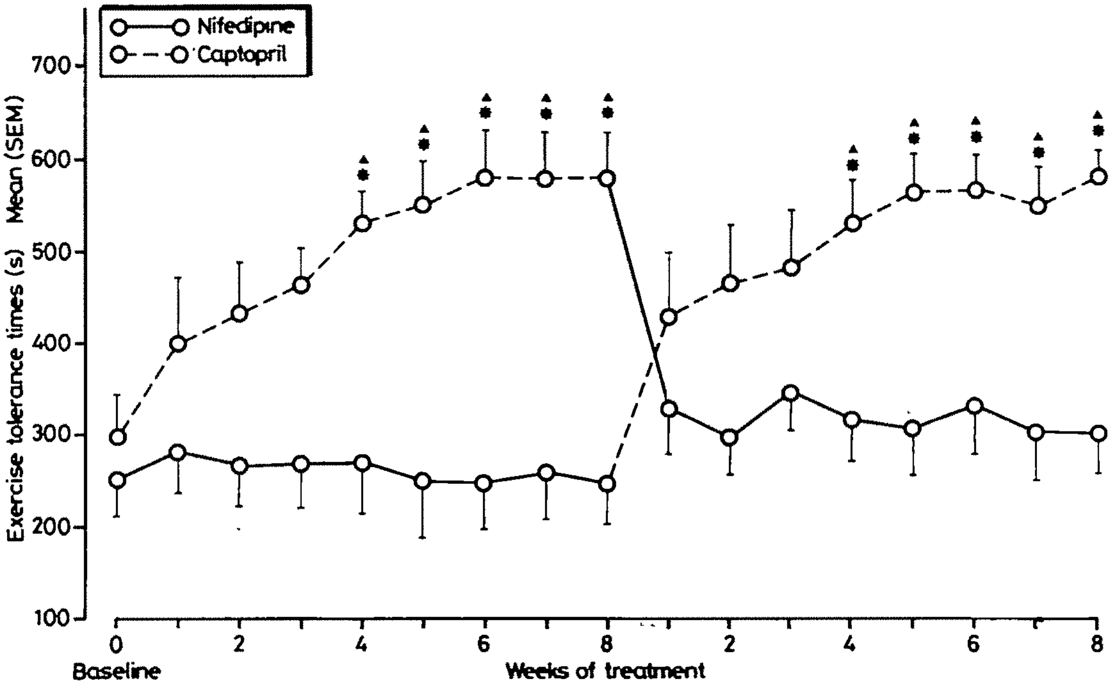

Fig. 2 *Comparison of times of maximal physical capacity during nifedipine and captopril treatments.* **Value significantly different from baseline value* ($p<0·01$); ▲ *Value significantly different from nifedipine treatment value* ($p<0·01$).

Table 2 *Clinical and humoral results with treatments in 18 patients with dilated cardiomyopathy*

| *Case* | *NYHA class* | | | *Body weight (kg)* | | | *Serum potassium (mmol/l)* | | | *Serum creatinine (mg/dl)* | | | *Dependent oedema* | | | *Symptoms that developed* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *B* | *N* | *C* | *B* | *N* | *C* | *B* | *N* | *C* | *B* | *N* | *C* | *B* | *N* | *C* | *N* | *C* |
| 1 | 4 | 4 | 3 | 58 5 | 58 | 57·2 | 3 8 | 3 5 | 4·1 | 1·8 | 2 0 | 2 2 | ++ | + | + | Headache, palpitation | — |
| 2 | 4 | 3 | 3 | 77 | 79·2 | 77 6 | 4 2 | 3 9 | 4·5 | 1 1 | 1 2 | 1 2 | + | +++ | + | Palpitation | — |
| 3 | 4 | 4 | 3 | 81 | 82 | 80 5 | 4 3 | 3 9 | 4 8 | 1 0 | 1 1 | 1 1 | + | +++ | + | Headache | |
| 4 | 3 | 4 | 3 | 81 6 | 83 | 78 2 | 3 7 | 3·3 | 4 2 | 1 9 | 1 4 | 1 6 | 0 | + | 0 | Palpitation | — |
| 5 | 3 | 3 | 2 | 74·4 | 75·4 | 72 2 | 3 5 | 3·3 | 4 0 | 1 7 | 1 5 | 2 2 | 0 | + | 0 | Headache, palpitation | — |
| 6 | 4 | 3 | 3 | 88 | 89 | 87 | 3 7 | 3 6 | 4 1 | 1 8 | 1·6 | 1 9 | ++ | ++ | + | — | — |
| 7 | 3 | 4 | 3 | 63 | 62·5 | 62 | 4·3 | 3 9 | 4 6 | 1·5 | 1·1 | 1 5 | + | + | 0 | Palpitation | — |
| 8 | 4 | 4 | 4 | 79 | 81 | 79 | 4 5 | 4 3 | 4 4 | 1 9 | 2 0 | 2 8 | ++ | +++ | + | Palpitation | — |
| 9 | 4 | 4 | 3 | 77 6 | 79 2 | 77 | 4 0 | 3 6 | 4 1 | 1·1 | 1·3 | 1 2 | + | +++ | + | — | Taste alteration |
| 10 | 4 | 4 | 4 | 85 8 | 85 6 | 85·7 | 4·1 | 4 1 | 4 5 | 1 2 | 1·3 | 1 1 | +++ | +++ | ++ | — | — |
| 11 | 4 | 3 | 3 | 86 | 87·5 | 84 8 | 3 6 | 3 3 | 4 1 | 1 9 | 1 7 | 1·8 | + | ++ | ++ | Palpitation | — |
| 12 | 3 | 3 | 3 | 80 5 | 81 6 | 77 9 | 4 3 | 4·1 | 4·7 | 1 8 | 1 9 | 2 2 | 0 | + | 0 | Palpitation | — |
| 13 | 4 | 4 | 3 | 76 | 78 8 | 76 5 | 4 4 | 4·1 | 4·7 | 1 6 | 1 8 | 2 2 | + | +++ | 0 | Headache | Taste alteration |
| 14 | 3 | 3 | 2 | 67 | 66 | 64·6 | 4 0 | 3 6 | 4 7 | 1 8 | 1 8 | 2 0 | 0 | 0 | 0 | — | — |
| 15 | 4 | 4 | 4 | 88 | 89 | 87 5 | 3·7 | 3·3 | 4 2 | 1 8 | 1 4 | 1 7 | ++ | +++ | ++ | Headache, palpitation | — |
| 16 | 3 | 4 | 3 | 61 4 | 65 | 60·3 | 4 4 | 4 1 | 4 7 | 1 4 | 1 6 | 1 1 | + | + | 0 | — | — |
| 17 | 3 | 3 | 2 | 65·4 | 65 | 64 | 3 6 | 3 3 | 4 1 | 1 2 | 1·5 | 1·5 | 0 | 0 | 0 | Palpitation | — |
| 18 | 4 | 4 | 3 | 73 | 76·3 | 72 | 3 9 | 3 9 | 4 3 | 1 5 | 1 7 | 1·7 | ++ | +++ | + | Palpitation | — |
| Means | 3 6 | 3 6 | 3 1* | 75 7 | 76 9* | 74 7 | 4·0 | 3 7 | 4 4* | 1 6 | 1 6 | 1·7 | — | — | — | — | — |
| SEM | 0·12 | 0 12 | 0 14 | 2 2 | 2 3 | 2 3 | 0 08 | 0 08 | 0 06 | 0 07 | 0 07 | 0 11 | | | | | |

*Significantly different ($p<0{\cdot}01$) from basal values.

B, basal, N, nifedipine, C, captopril; NYHA, New York Heart Association.

lar resistance and was associated with a 12% rise in cardiac index. Mean pulmonary arterial pressure, pulmonary arteriolar resistance, and the pulmonary capillary wedge pressure tended to decrease, although these changes were not statistically significant. After long term treatment the response was substantially different. In fact, changes from baseline in mean arterial pressure, and cardiac index were less pronounced and were no longer statistically significant; heart rate and pulmonary capillary wedge pressure showed a clear tendency to increase.

The response to oral captopril was also greatest approximately 1·5 h after administration. In five patients the first dose induced considerable increases in cardiac index and stroke volume index and decreases in mean arterial pressure, heart rate, systemic vascular resistance, and pulmonary capillary wedge pressure, which were sustained after eight weeks of continuous treatment. Four patients had minimal haemodynamic responses to the first 50 mg of the drug and also showed small changes when up to three times this dose was given. Despite the reduced initial response they continued on the standard protocol and were treated with the standard dosage. Repeat assessment after eight weeks of continuous treatment showed a spontaneous improvement of efficacy in three patients, in whom values became similar to those of the early responders in the same group. Because of this pattern, which has been reported by others,[15 16] overall haemodynamic changes from baseline that were present in the short term study were much more pronounced at long term re-evaluation (Fig. 3).

Figure 4 shows means for the circulatory variables that were recorded in the entire population at baseline and after long term treatment with both agents. The changes induced by captopril and nifedipine moved in the same direction, as shown in Fig. 3. This indicates that the sequence of drug administration did not interfere with the quality of the response to the treatments. Cardiothoracic ratios measured by independent observers on standard chest *x* rays were significantly reduced after captopril. The mean control ratio was 0·575 compared with a mean ratio of 0·560 after two months of captopril treatment ($p<0{\cdot}01$).

Left ventricular end systolic circumferential wall stress (mean for the entire population with the exception of six patients) was significantly reduced by captopril and to a lesser extent and not significantly by nifedipine at the end of the treatment period; the force-length relation was shifted to the left after captopril but not after nifedipine (Fig. 5).

No patients had to stop taking captopril or nifedipine during the study because of adverse reactions (Fig. 1).

While on nifedipine five patients complained of headache and 11 reported palpitation that was described as disturbing by six. We do not know whether this symptom was associated with wors-

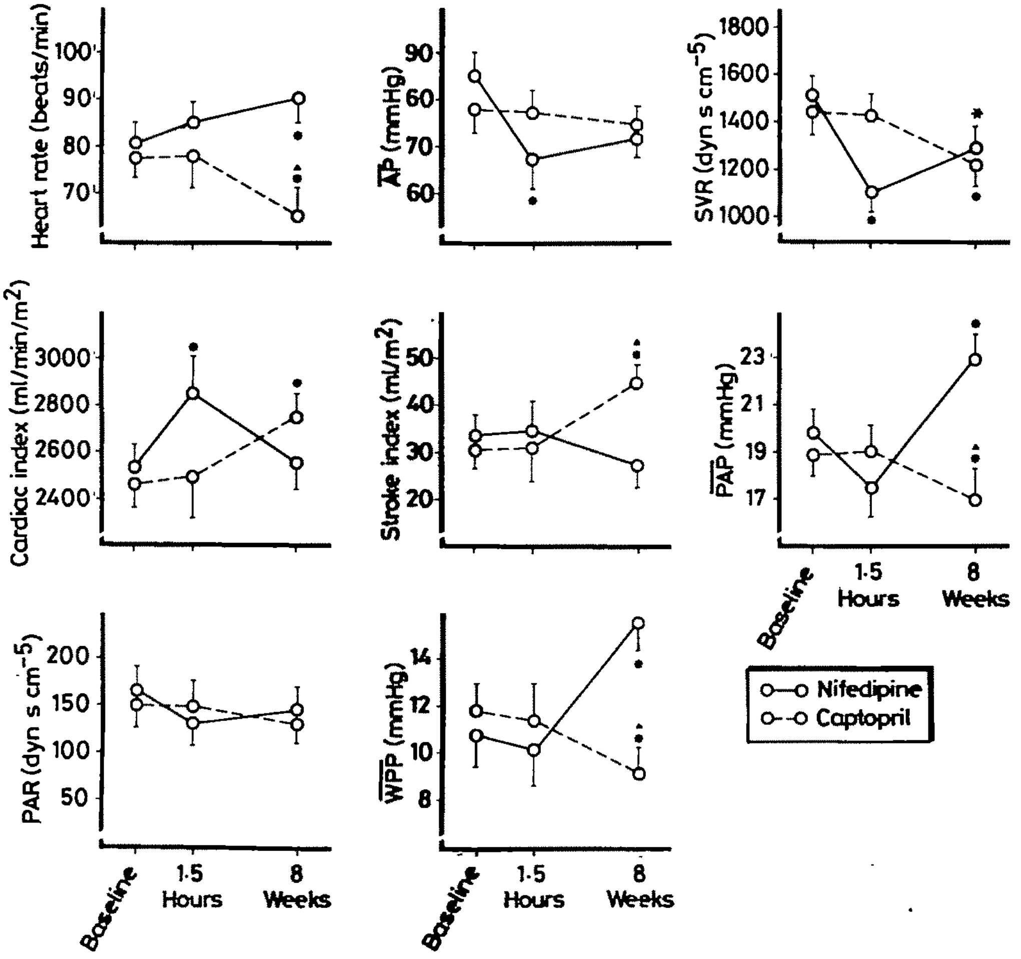

Fig. 3 *Haemodynamic values (mean (SD)) at baseline, after 1·5 hours, and after eight weeks of treatment in patients given captopril (nine cases) and nifedipine (nine cases) as the first drug. $\overline{AP}$, mean arterial pressure; SVR, systemic vascular resistance; PAR, pulmonary arteriolar resistance; $\overline{WPP}$, mean pulmonary capillary wedge pressure; $\overline{PAP}$, mean pulmonary arterial pressure. *Value significantly different from baseline value ($p<0{\cdot}01$); ▲ Value significantly different from nifedipine treatment value ($p<0{\cdot}01$).*

ening arrhythmia because we did not evaluate this. We also found an increase in body weight in 12 patients and enhancement of dependent oedema in 11 while they were on nifedipine. This latter effect, however, may not necessarily be due to cardiac causes.[17] Nifedipine also reduced mean serum potassium concentration and did not depress renal function (Table 2).

Captopril did not lead to the development of dependent oedema or increase body weight. Two patients on this treatment complained of a slight and transient taste alteration; in one patient serum creatinine concentration rose from 1·9 to 2·8 mg/dl; mean serum potassium rose from a baseline concentration of 4·0 mmol/l to 4·4 mmol/l ($p<0{\cdot}01$); this was also significantly higher than the concentration (3·7 mmol/l) on nifedipine (Table 2).

## Discussion

In this study two potent vasodilators with different mechanisms of action were used to treat heart failure due to cardiomyopathy. Captopril or nifedipine were given with a fixed regimen of digitalis and diuretics in a double blind crossover trial. Captopril significantly improved the New York Heart Association functional class and exercise tolerance times. The incorporation of captopril into conventional

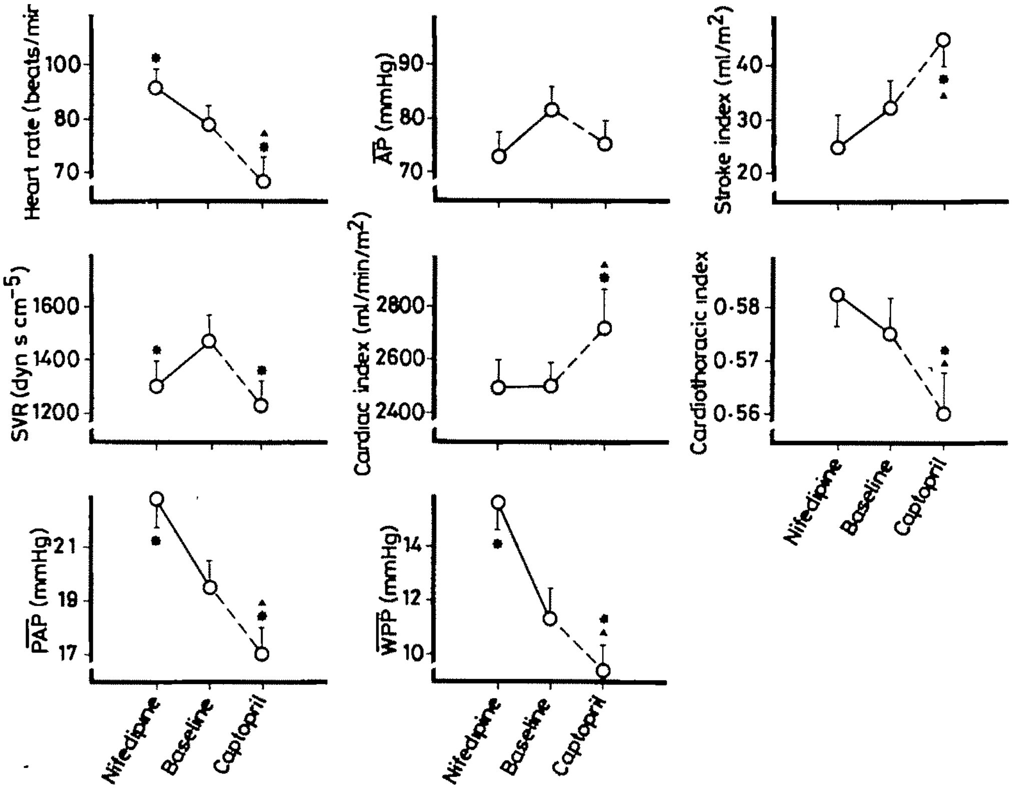

Fig. 4 *Haemodynamic values (mean (SD)) of the entire population at baseline and after eight weeks' treatment with captopril and nifedipine. $\overline{AP}$, mean arterial pressure; SVR, systemic vascular resistance; $\overline{PAP}$, mean pulmonary arterial pressure; $\overline{WPP}$, mean pulmonary capillary wedge pressure. *Value significantly different from baseline value ($p<0{\cdot}01$); ▲ Value significantly different from nifedipine treatment value ($p<0{\cdot}01$).*

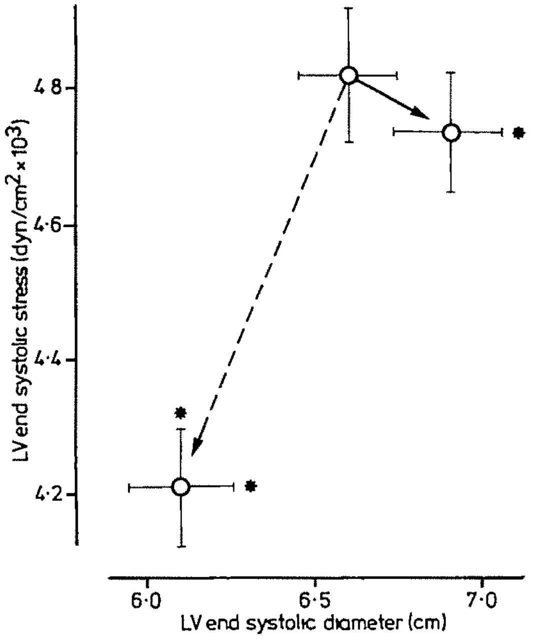

Fig. 5 *Relation between left ventricular end systolic wall stress and left ventricular end systolic internal diameter at baseline and after eight weeks' treatment with captopril (broken arrow) and after eight weeks' treatment with nifedipine (solid arrow) Circles represent the means and lines the SD. *$p<0{\cdot}01$ for differences in wall stress and diameter between baseline and treatment.*

heart failure treatment permitted patients who were incapacitated by symptoms to perform at least a moderate physical exertion. A training effect is unlikely to be responsible for this result because the physical tests were of short duration and infrequent. Nifedipine did not relieve symptoms, and made some patients worse. In the long term trial the significant reduction of the pulmonary capillary wedge pressure and the increase of cardiac output by captopril but not by nifedipine showed that at least part of the increased functional capacity might be the result of an improved performance of the left ventricle.

Did vasodilating potency or some other factor influence responses to the two drugs? In the short term study systemic vascular resistance was consistently reduced by nifedipine, cardiac output was raised, and the left ventricular filling pressure tended to fall. This pattern was similar to the response to nifedipine reported in patients with dilated cardiomyopathy and acute pulmonary oedema.[5-7] During prolonged treatment, however, cardiac output did not improve and the pulmonary capillary wedge pressure rose substantially, indicating that the benefits of the reduced impedence to left ventricular ejection observed in the short term study were lost, even though the vasodilating action of nifedipine persisted. Changes in systemic vascular resistance after prolonged administration of captopril resembled those produced by nifedipine, but captopril improved the performance of the left ventricle, as indicated by the filling pressure-cardiac output relation.

Heart rate was increased (by an average of nine beats/min) on nifedipine and reduced (by an average of 11 beats/min) on captopril. This finding may be relevant to the different haemodynamic effects of the two agents since the greater the dysfunction of a ventricle the higher its sensitivity to changes in afterload.[18] Also when the cavity becomes enlarged and systolic wall thickening is diminished, as in dilated cardiomyopathy, ventricular dimension becomes an important determinant of afterload. In such a situation, if cardiac output remains constant, afterload may vary in parallel with heart rate, because the ventricular cavity is reduced more during systole when heart rate is slow than when it is fast. Indeed captopril treatment was associated with an increased stroke index.

End systolic stress represents the critical afterload value which terminates ventricular ejection[19] and measurement of end systolic stress is a good index of the role of afterload in determining ventricular pump function. We assessed end systolic left ventricular circumferential wall stress by a non-invasive method, although we were aware that echocardiographic measurements in patients with dilated hearts are liable to error and that the reproducibility may be unsatisfactory. In order to improve the reliability and reproducibility of such measurements we used appropriate techniques and criteria of recording, coded the echocardiograms, read them blindly and in random order, and took the average of triplicate measurements for each period. The correspondence in most cases between changes in ventricular cavity dimensions evaluated by ultrasound and changes in cardiothoracic ratio, and the uniformity of the trends during treatment indicate that our echocardiographic records were reliable.

The minor axis of the left ventricle at end systole was significantly reduced by captopril but not by nifedipine, and end systolic afterload was reduced by captopril and not by nifedipine (Fig. 5), even though the reduction of systemic vascular resistance and possibly of aortic impedence was similar with the two treatments.

The leftward shift of the force-length relation after captopril may indicate either a shift to a different point in the same basal stress-length line (which would indicate no change in contractility) or a displacement to the left of the force-length line itself (which would indicate improved contractility).[13 14] This relation tended to move rightward when patients were treated with nifedipine, indicating that some depression in contractility may have occurred.

The reduction in heart rate with captopril, which has been reported in several previous studies,[9 16 20] may be due to the absence of a facilitating action of angiotensin II on the sympathetic neurotransmission,[21] or to reduction of catecholamine release,[17] or to venodilatation. Captopril causes both venodilatation and arteriolar dilatation and hence heart rate may remain constant.[17] If the adrenergic drive to the heart were really depressed by captopril when there was a concomitant improvement in cardiac function, the hypothesis advanced by some[22] that catecholamines are deleterious in primary cardiomyopathies would be reinforced.

In conclusion, the therapeutic efficacy and low frequency of important adverse effects indicate that captopril is useful in patients with decompensated dilated cardiomyopathies that are refractory to conventional treatment. The poor or adverse responses to nifedipine that we have reported in this study discourage its use in such patients.

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# Echocardiographic evaluation of verapamil in Friedreich's ataxia

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SUMMARY Nine patients with hypertrophic cardiomyopathy associated with Friedreich's ataxia were treated with the calcium antagonist verapamil, which is known to reduce myocardial hypertrophy and improve diastolic function in patients with idiopathic hypertrophic cardiomyopathy. Daily oral doses of 7 mg/kg were given for a mean (SD) of 24 (8) months. M mode echocardiography performed at the start of the study and at the end of follow up showed no significant difference between the treated group and an untreated control group of nine patients. Verapamil produced no changes in left ventricular wall thickness, mass index, left ventricular internal diameter, fractional shortening, peak normalised lengthening rate, peak rate of septal and posterior wall thinning, and time from minimum ventricular cavity dimension to mitral valve opening.

Myocardial calcium overload has been suggested as a cause of cardiac disease in Friedreich's ataxia; however, verapamil had no beneficial effect on these patients with established myocardial hypertrophy.

Left ventricular hypertrophy (usually concentric and non-obstructive) has been found in 38% to 67% of patients with Friedreich's ataxia.[1-3] In a series of 18 cases our own group found echocardiographic evidence of concentric left ventricular hypertrophy in 39% of cases and asymmetric (non-obstructive) hypertrophy in 33%.[4] St John Sutton *et al* found reduced diastolic function in most of their patients with Friedreich's ataxia.[5]

Calcium antagonists have been effective in other forms of hypertrophic cardiomyopathy. Kaltenbach *et al* gave oral verapamil (480 mg daily) for more than a year to patients with obstructive hypertrophic cardiomyopathy.[6] They found that QRS voltage, heart volume (determined radiologically), and left ventricular mass (determined haemodynamically) were reduced. Hirzel *et al* confirmed these findings[7]; as did Spicer *et al* in children.[8] Verapamil has also been reported to improve left ventricle relaxation and filling in adults and children with hypertrophic cardiomyopathy.[8-10]

Other evidence encourages the use of calcium antagonists for cardiomyopathy. Sanchez-Casis *et al* described granular calcium and iron deposits in degenerate myocardial fibres in a patient with Friedreich's ataxia.[11] Lamarche *et al*, however, did not confirm this finding in an electron microscope study of three cases.[12] It has been suggested but not confirmed that the cardiomyopathy associated with Friedreich's ataxia may be the result of defective calcium transport through cell membranes with subsequent accumulation in the fibres.[13-14] These reports prompted us to study the long term effect of verapamil on cardiomyopathy in patients with Friedreich's ataxia.

## Patients and methods

Thirteen patients with Friedreich's ataxia diagnosed by Geoffroy's criteria[15] entered the trial. In all of them left ventricular hypertrophy of various grades of severity was seen on M mode echocardiography, and none of them had any contraindications to long term calcium antagonist treatment. They all gave their informed consent. Two patients dropped out within two months because of hypotension, another abandoned treatment, and a fourth did not report for follow up examinations after 7 months. The nine remaining patients (group 1) (5 male and 4 female),

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Accepted for publication 3 December 1985

Table 1 *Echocardiographic variables used to assess effect of verapamil treatment on heart muscle*

| *Variable* | *Abbreviation* |
|---|---|
| (1) Interventricular septum thickness | IVSTh |
| (2) Left ventricular posterior wall thickness | LVPWTh |
| (3) IVSTh/LVPWTh ratio | — |
| (4) Left ventricular end diastolic diameter | LVEDD |
| (5) Left ventricular end systolic diameter | LVESD |
| (6) Left ventricular mass index | LV mass index |
| (7) Left ventricular fractional shortening | FS% |
| (8) Left atrium:aorta ratio | LA:AO |
| (9) Time from minimum left ventricular cavity dimension to the onset of mitral valve opening | LVESD–MVO |
| (10) Peak normalised lengthening rate | Lng rate |
| (11) Peak rate of septal thinning | dSd/dt |
| (12) Peak rate of posterior wall thinning | dWd/dt |

were aged from 10 to 34 years (mean age (SD) 21·9 (7·5)), with body surfaces between 1·05 and 1·8 m$^2$ (mean (SD) area 1·43 (0·27)). Another nine patients with the same condition (group 2) served as controls. There were 6 male and 3 female patients aged from 10 to 36 years old (mean (SD) age 20·3 (8·1)), with body surfaces between 0·9 and 1·8 m$^2$ (mean (SD) area 1·45 (0·24)). Patients had cardiological examinations every three months for 13 to 37 months in group 1 (mean (SD) 24 (8·4) months) and 10 to 49 months in group 2 (mean 24 (SD) 13 months). Age, body surface area, and length of follow up were similar in the two groups. Echocardiographic findings of groups 1 and 2 were compared with those of 25 normal subjects (group 3) of similar mean (SD) age (20·6 (9·7) years) and body surface area (1·44 (0·15) m$^2$). Patients took verapamil (7 mg/kg daily) as two or three separate oral doses. Venous blood samples were taken from seven of the nine patients within four to six hours of a dose of verapamil and were assayed for unchanged drug and metabolites (norverapamil $D_{617}$ to $D_{620}$). Blood concentrations (mean (SD) 128 (118) ng/ml) were within therapeutic range (41 to 327 ng/ml).

Table 1 shows echocardiographic variables that we used to assess the effect of verapamil treatment on the heart muscle. Each patient was examined by M mode echocardiography on at least three occasions. Echocardiograms were obtained with a commercially available machine equipped with a 0·5 cm transducer, ultrasound frequency 2·25 MHz, connected to a paper printout unit (chart speed 25 or 50 mm/sec), and an electrocardiogram was recorded simultaneously. All echocardiographic examinations were conducted by the same cardiologist who followed the recommendations of the Workshop of the European Society of Cardiology,[16] and paid special attention to the left and right endocardium of the interventricular septum and posterior wall of the left ventricle. Tracing reproducibility was ensured by consistent use of the same echocardiographic window with the patient in the same position. Left ventricular mass was calculated by the Devereux equation and Penn's convention.[17] Left ventricular volume was calculated by the cube formula. All tracings were technically adequate for calculation of variables 1 to 8 (Table 1).

Left ventricular diastolic function was assessed from a digitised M mode echocardiogram recorded at 50 mm/s chart speed. Six of nine echocardiograms in group 1 and seven of nine in group 2 were suitable for computer analysis. For each case we digitised three consecutive cardiac cycles with clearly identifiable septal endocardial and posterior wall endocardial echoes. The M mode cursor was positioned over the left ventricle to provide best imaging of the interventricular septum, posterior wall of the left ventricle, and separation of mitral valve leaflets. The point of mitral valve opening was identified. Digital conversion was done with a hand operated graphic tablet (Hewlett-Packard 9111A); digital data were processed by a Hewlett-Packard 1000 computer system that gives instantaneous plots of left ventricular internal dimension, septal and posterior wall thickness, and the rate at which they are changing. Variables 9 to 12 (Table 1) were calculated by computer analysis. Peak normalised lengthening

Table 2 *Statistical comparison (Kramer test) of echocardiographic variables in patients with Friedreich's ataxia treated with verapamil (group 1), untreated patients (group 2), and healthy subjects (group 3)*

| *Variable* | *Group 1 vs* | *Group 3* | *p* | *Group 2 vs* | *Group 3* | *p* | *Group 1 vs* | *Group 2* | *p* |
|---|---|---|---|---|---|---|---|---|---|
| IVSTh (mm) | 11 1 (1 4) | 6 5 (1·0) | <0 01 | 10 2 (1 3) | 6 5 (1 0) | <0 01 | 11·1 (1·4) | 10·2 (1·3) | NS |
| LVPWTh (mm) | 10 9 (1 6 | 6 1 (1 2) | <0 01 | 10 0 (0 8) | 6 1 (1·2) | <0 01 | 10·9 (1 6) | 10 0 (0 8) | NS |
| IVS/LVPW | 1 0 (0 2) | 1 1 (0 2) | NS | 0 9 (0 1) | 1 1 (0·2) | NS | 1·0 (0 2) | 0 9 (0·1) | NS |
| LVEDD (mm) | 38 4 (5 3) | 44 8 (4 2) | <0 01 | 41 5 (4 6) | 44·8 (4 2) | NS | 38·4 (5·3) | 41 5 (4 6) | NS |
| LVESD (mm) | 25 2 (5 7) | 26 9 (3 4) | NS | 26·5 (4·5) | 26 9 (3 4) | NS | 25 2 (5·7) | 26·5 (4 5) | NS |
| LV mass index (g/m$^2$) | 111 9 (26) | 62 5 (16) | <0·01 | 112·8 (18) | 62 5 (16) | <0·01 | 111·9 (26) | 112·8 (18) | NS |
| FS% | 34 1 (8 3) | 39 7 (4 8) | <0 05 | 36·2 (7·6) | 39 7 (4 8) | NS | 34 1 (8 3) | 36·2 (7 6) | NS |
| LA/AO | 1·1 (0·1) | 1·1 (0 1) | NS | 1 1 (0 2) | 1·1 (0 1) | NS | 1·1 (0·1) | 1 1 (0·2) | NS |
| Body surface area (m$^2$) | 1 4 (0 3) | 1·4 (0 1) | NS | 1 4 (0 3) | 1·4 (0·1) | NS | 1 4 (0 3) | 1 4 (0·3) | NS |

See Table 1 for abbreviations.

Table 3 *Statistical comparison (Kramer test) of echocardiographic variables in left ventricular diastolic function and relaxation in patients with Friedreich's ataxia treated with verapamil (group 1), untreated patients (group 2), and healthy subjects (group 3)*

| *Variable* | *Group 1* | *vs* | *Group 3* | *p* | *Group 2* | *vs* | *Group 3* | *p* | *Group 1* | *vs* | *Group 2* | *p* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| LVESD–MVO (ms) | 57 (26) | | 55 (27) | NS | 28 (39) | | 55 (27) | NS | 57 (26) | | 28 (39) | NS |
| Lng rate ($s^{-1}$) | 3·7 (0·6) | | 5·0 (1·6) | NS | 4·0 (0·9) | | 5·0 (1·6) | NS | 3·7 (0·6) | | 4·0 (0·9) | NS |
| dSd/dt (cm/s) | 4·3 (1·4) | | 6·8 (2·3) | <0·05 | 4·5 (1·6) | | 6·8 (2·3) | <0·05 | 4·3 (1·4) | | 4·5 (1·6) | NS |
| dWd/dt (cm/s) | 6·7 (1·9) | | 12 (3·3) | <0·01 | 7·2 (3·2) | | 12 (3·3) | <0·01 | 6·7 (1·9) | | 7·2 (3·2) | NS |

See Table 1 for abbreviations.

rate and peak rate of septal and posterior wall thinning were used to assess diastolic function.[18] Time from minimum left ventricular cavity dimension to onset of mitral valve opening was used as an index of left ventricular relaxation. We did not measure the isovolumic relaxation time (that is the interval between the second heart sound and mitral valve opening) because in some cases an accompanying phonocardiogram was not available; also, this interval has been reported to be an unreliable indicator of ventricular relaxation in patients with hypertrophic cardiomyopathy.[19]

We used the Kramer test[20] and covariance analysis[21] for statistical analysis; the former is suitable for comparison of means from groups of unequal sizes and the latter for adjusting values obtained at the end of follow up so that the influence of differences between the initial means for the two groups is eliminated.

## Results

Tables 2 and 3 show the echocardiographic data from patients with Friedreich's ataxia treated with verapamil (group 1), data from similar patients not receiving treatment (group 2), and data from normal subjects (group 3).

Patients with Friedreich's ataxia (groups 1 and 2) had significantly ($p<0\cdot01$) thicker interventricular septal and posterior left ventricular walls. They also had significantly ($p<0\cdot01$) higher left ventricular mass indices and significantly ($p<0\cdot01$) slower peak rates of posterior wall thinning. Peak rates of septal thinning were significantly ($p<0\cdot05$) slower in patients with Friedreich's ataxia than in normal subjects. The end diastolic diameter of the left ventricle was significantly smaller in patients of group 1 than in group 3, but there was no significant difference between groups 2 and 3. The left ventricular fractional shortening was significantly less in patients in group 1 (but not in patients in group 2) than in group 3 ($p<0\cdot05$).

There were no differences between groups for time from minimum left ventricular cavity dimension to onset of mitral valve opening or for peak lengthening rates. Tables 4 and 5 summarise the initial and final echocardiographic findings obtained in patients of groups 1 and 2. Palpitation in one patient and recurrent headache in another abated while they were on verapamil. None of the patients developed evidence of heart failure during long term verapamil treatment.

## Discussion

Our results are at variance with those reported by other workers who used similar doses of verapamil to treat patients with hypertrophic cardiomyopathy.[5,6,8,22] We found that long term treatment with verapamil of patients with cardiomyopathy as-

Table 4 *Statistical comparison (covariance analysis*) of echocardiographic variables at the beginning and at the end of follow up in patients who were treated with verapamil and those who were not*

| *Variable* | *Before verapamil* | | | *After verapamil* | | |
|---|---|---|---|---|---|---|
| | *Group 1* | *vs* | *Group 2* | *Group 1* | *vs* | *Group 2* |
| IVSTh (mm) | 11·1 (1·4) | | 10·2 (1·3) | 11·1 (1·8) | | 10·3 (1·3) |
| LVPWTh (mm) | 10·9 (1·6) | | 10·0 (0·8) | 11·1 (1·9) | | 9·4 (1·1) |
| IVS/LVPW | 1·0 (0·2) | | 0·9 (0·1) | 1·0 (0·1) | | 1·1 (0·1) |
| LVEDD (mm) | 38·4 (5·3) | | 41·5 (4·6) | 40·4 (5·0) | | 42·5 (6·5) |
| LVESD (mm) | 25·2 (5·7) | | 26·5 (4·5) | 26·5 (5·1) | | 27·0 (6·4) |
| LV mass index (g/m²) | 111·9 (26) | | 112·8 (18) | 124·3 (41) | | 108·1 (17) |
| FS% | 34·1 (8·3) | | 36·2 (7·6) | 35·1 (5·7) | | 36·8 (7·6) |
| LA/AO | 1·2 (0·1) | | 1·1 (0·2) | 1·1 (0·1) | | 1·1 (0·2) |

*None of the variables was significantly different.
See Table 1 for abbreviations.

Table 5 *Statistical comparison (covariance analysis*) of echocardiographic variables of left ventricular diastolic function and relaxation at the beginning and at the end of follow up in patients treated with verapamil (group 1) and those who were not (group 2)*

| *Variable* | *Before verapamil* | | | *After verapamil* | | |
|---|---|---|---|---|---|---|
| | *Group 1* | *vs* | *Group 2* | *Group 1* | *vs* | *Group 2* |
| LVESD–MVO (ms) | 57 (26) | | 28 (39) | 44 (14) | | 31 (33) |
| Lng rate ($s^{-1}$) | 3·7 (0·6) | | 4·0 (0·9) | 5·1 (1·5) | | 4·1 (1·6) |
| dSd/dt (cm/s) | 4·3 (1·4) | | 4·5 (1·6) | 5·7 (2·6) | | 4·1 (1·2) |
| dWd/dt (cm/s) | 6·7 (1·9) | | 7·2 (3·2) | 9·8 (4·5) | | 6·8 (2·7) |

*None of the variables was significantly different.
See Table 1 for abbreviations

sociated with Friedreich's ataxia produced no detectable difference by echocardiography between treated and untreated patients after mean follow up of two years. Our findings do, however, accord with those of Rosing *et al* who did not see any significant reduction of septal or posterior wall thickness in the left ventricle of 31 patients treated by long term administration of verapamil and followed up for at least one year.[23] The reduction of left ventricular thickness reported by Kaltenbach *et al*, by Kuhn *et al*, and by Spicer was <2 mm and was sometimes only of borderline significance.[6 8 22]

Our results do not support the hypothesis that intramyocardial calcium accumulation is an important factor in the pathogenesis of cardiac disease in Friedreich's ataxia. Although the hypothesis rests on apparently good experimental evidence, the fact remains that verapamil did not reduce established myocardial hypertrophy. The role of calcium accumulation in the pathogenesis of myocardial hypertrophy in patients with Friedreich's ataxia can probably only be established by a study in which verapamil is given early in the course of disease, when neurological and cardiac signs and symptoms are just beginning to appear—that is, before myocardial cells are replaced by fibrotic tissue.[9 24]

Our data on basal diastolic function accord broadly with those reported by St John Sutton *et al* in a study of seven patients with Friedreich's ataxia.[5] All patients with hypertrophic cardiomyopathy (groups 1 and 2) had a highly significant reduction of the posterior wall thinning peak rate and a significant reduction in septal thinning rate compared with normal subjects. The peak rate of left ventricular lenthening, on the other hand, was not significantly reduced (in St John Sutton's series this variable was slightly less than normal values in two of seven cases). Unlike St John Sutton *et al* we did not find that the time from minimum left ventricular cavity size to onset of mitral valve opening was significantly increased.

We found that oral verapamil had no beneficial effects in group 1, not even on the diastolic indices of left ventricular function. This finding is seldom referred to in published reports, and only then in patients with hypertrophic cardiomyopathy other than Friedreich's, and also chiefly in connection with studies of the short term effects of the drug. Even in this limited area, the results of various studies are not in complete accord.[9 25 26]

In conclusion, long term oral treatment with verapamil at high doses was readily tolerated by all our patients. In particular, there was no deterioration of left ventricular systolic function or evidence of heart failure. Verapamil, a calcium antagonist, did not reduce left ventricular wall thickness, possibly because interstitial fibrosis in these patients with Friedreich's ataxia was already advanced. Left ventricular diastolic function was not significantly improved by long term verapamil treatment.

In our opinion routine verapamil treatment is not justified in symptom free patients who have Friedreich's ataxia complicated by hypertrophic cardiomyopathy. Alone or in association with other drugs, however, verapamil might be useful in the treatment of supraventricular tachyarrhythmia in selected cases.

We thank Mrs Loredana Parinello for the statistical analysis, and Dr R Padrini for the blood verapamil assays.

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*Br Heart J* 1986; 55: 405–7

## *Case reports*

# Cross sectional echocardiographic appearance in presumed congenital absence of the left pericardium

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SUMMARY An unusual and new cross sectional echocardiographic feature, bulging of the inferior left ventricular wall during diastole, is described in a 35 year old woman with congenital total absence of the left pericardium. The diagnosis was made on the characteristic clinical, electrocardiographic, echocardiographic, and radiological findings.

Congenital absence of the left pericardium was thought to be uncommon, and up to about 10 years ago was usually only diagnosed by surgeons and pathologists. The clinical diagnosis from the combination of physical examination, electrocardiogram, and chest radiograph has been reported.[1 2] We present a patient in whom absence of the left pericardium was diagnosed clinically and by cross sectional echocardiography.

## Case report

A 35 year old woman was referred to the cardiology department because of the unusual appearance of a chest radiograph taken before an operation for chronic otitis media. She complained of mild symptoms of atypical chest pain and dyspnoea on exertion for four years. Her blood pressure was 130/80 mm Hg and the pulse rate was 80 beats/minute and regular. She was in no distress. The apical impulse was located in the mid axilla and was prominent. There was a grade 1/6 systolic ejection murmur at the pulmonary area. The second heart sound was widely split, but not fixed. The electrocardiogram showed right axis deviation and leftward displacement of the transition zone in the precordial leads. The chest radiograph showed an unusual bulging on the apical area. Left lateral chest radiograph and tomograms showed interposition of lung tissue between the inferior border of the heart and the left hemidiaphragm (Fig. 1). A similar finding was also shown by a radionuclide perfusion image of the lung.[3] On M mode echocardiography there was reversed movement of the interventricular septum. Cross sectional echocardiographic examination showed that the dimensions of both ventricles were normal. At the level of the apex beyond the mitral valve (Fig. 2) there was a bulge on the lateral mid-inferior and inferior walls at the end of diastole and a return to normal during systole. No other abnormal features were seen. The patient did not give her consent for either an artificial pneumothorax or cardiac catheterisation.

## Discussion

Congenital absence of the left pericardium is a rare condition. It may be diagnosed on the basis of clinical signs and electrocardiographic and radiographic findings. The performance of an artificial pneumothorax, to confirm the diagnosis is unwarranted.[1 2] Cardiac catheterisation with angiography is useful when the diagnosis is in doubt or when surgical management is necessary, especially for partial absence.[1 2] The M mode echocardiographic features of the congenital complete absence of the left pericardium, which are dilatation of the right ventricle and paradoxical interventricular septal motion are not diagnostic of this lesion. They may be seen in various conditions, such as atrial septal defect, partial anomalous pulmonary

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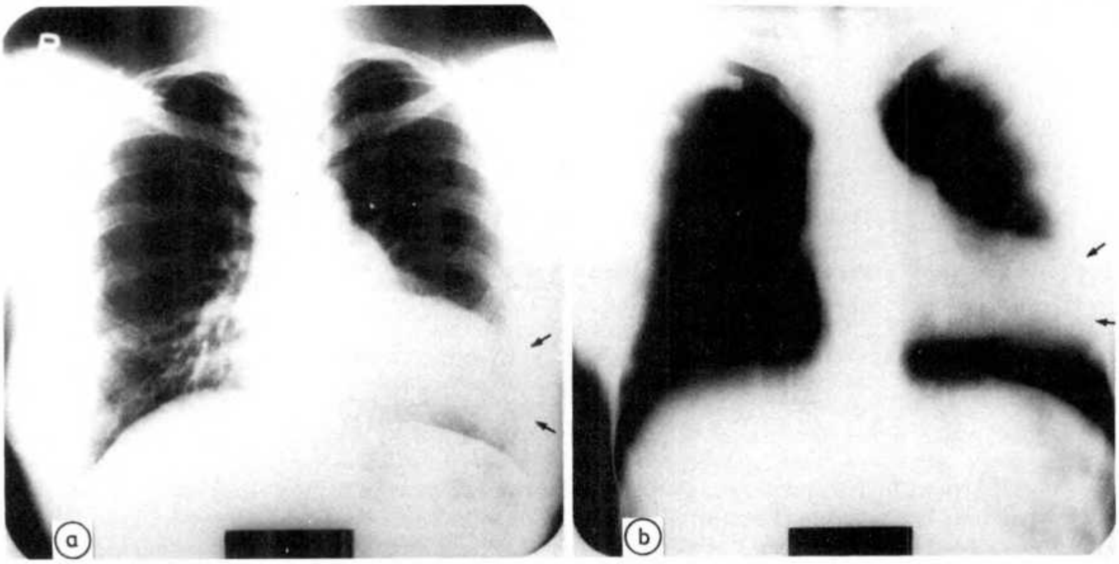

Fig. 1 *(a) Chest radiograph and (b) tomogram showing prominent pulmonary artery and the interposition of lung tissue between the inferior border of the heart and the left hemidiaphragm. Unusual bulging of the apical area is indicated by arrows.*

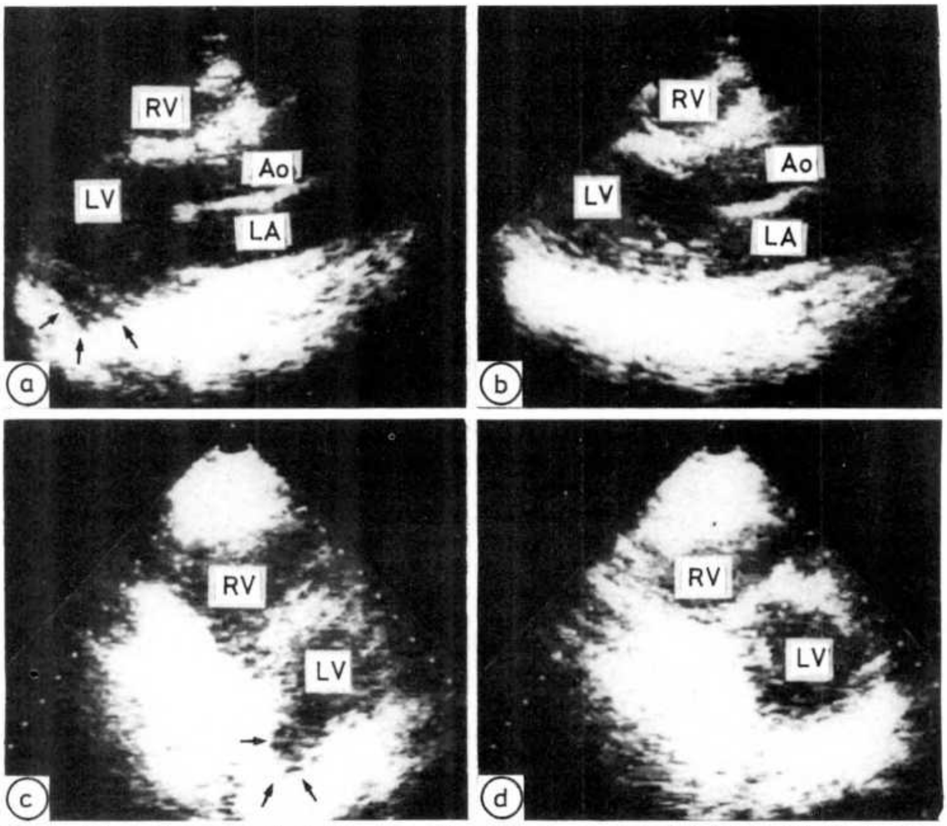

Fig. 2 *Echocardiograms in the (a) parasternal long axis view at the end of diastole and (b) the same view at end systole. Note the bulging (arrows) of the lateral inferior wall. (c) Parasternal short axis view at the apex at end diastole and (d) the same view at end systole. Note the same bulging of the inferior wall (arrows). The bulging is not present in (b) and (d). Ao, aorta; LA, left atrium; LV, left ventricle; RV, right ventricle.*

venous connection, tricuspid regurgitation, and after cardiac surgery.[4] None the less, M mode echocardiography is useful for differentiating these conditions when it is used as an adjunct to cross sectional echocardiography. Recently, Rowland *et al* described the cross sectional echocardiographic findings in a patient with partial absence of the left pericardium.[5] Nicolosi *et al* reported cross sectional echocardiographic findings in two patients with absence of the left pericardium. These were caused by lateral rotation and excessive cardiac motion and were consistent with the M mode features.[6] To our knowledge, this is the first report showing a very unusual feature of a congenital total absence of the left pericardium on cross sectional echocardiography. The bulging seen on the inferior wall may mimic a ventricular aneurysm, but unlike an aneurysm this appearance was most prominent during diastole and disappeared during systole. On the other hand, this localised abnormality of the left ventricular contour with normal right ventricular dimensions can help to distinguish patients with congenital absence of pericardium from those with right ventricular volume overload.

We thank Aytekin Besim and Emin Alp Niron for drawing our attention to this case.

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*Br Heart J* 1986; 55: 408–10

# Myocardial infarction after blunt chest trauma incurred during rugby football that later required cardiac transplantation

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SUMMARY A 28 year old man sustained an extensive anterolateral myocardial infarction five minutes after a blow on the chest while playing rugby football. The resulting persistent cardiac failure necessitated orthotopic cardiac transplantation.

Blunt trauma to the chest may result in various cardiac injuries,[1] including myocardial infarction. Such cardiac injury is most commonly seen after road traffic accidents, due to impact of the chest on the steering wheel. Cardiac injury may also result from other types of blunt chest trauma. There are reports of such injuries occurring during sporting activities including cricket,[2] association football,[3 4] horse-riding,[5] softball,[6] boxing,[7] and basketball.[8] We report a case of myocardial infarction in a young man that occurred minutes after he received a blow on the chest while playing rugby. We have not found any other reports of a similar injury in which myocardial infarction occurred and was subsequently treated by cardiac transplantation.

## Case report

A 28 year old man developed severe central chest pain associated with dyspnoea and sweating about five minutes after receiving a blow to the chest during a high tackle while playing rugby football. He was admitted to a local hospital where he was found to be hypotensive and to have pulmonary oedema. Myocardial infarction was diagnosed.

The next day he was transferred to this hospital because of evidence of persisting cardiogenic shock with left ventricular failure despite treatment with diuretics and intravenous inotropic support. On admission he was restless, sweating, had low volume pulses, and a blood pressure of 80/60 mm Hg. There was clinical and radiological evidence of severe pulmonary oedema. There was no evidence of pericardial fluid on echocardiography. Serial electrocardiograms showed the changes of an acute anterolateral myocardial infarction with reciprocal changes in the inferior limb leads (Fig. 1). Serial cardiac enzyme concentrations were considerably increased (peak creatine kinase being 8693 IU/l). There was no sternal abnormality or sign of external injury.

Treatment with diuretics and intravenous and oral inotropes was continued and vasodilator treatment including angiotensin-converting enzyme inhibitors was added. Daily urine output was 650–1300 ml/24 h during the first week of admission. Mean pulmonary capillary wedge pressure during this period was in the range 14–20 mm Hg. Cardiac output was not measured. He slowly improved over about three weeks, although evidence of pulmonary oedema persisted. He had several episodes of pulmonary thromboembolism and was given anticoagulants. Recurrent episodes of ventricular tachycardia were successfully treated with amiodarone. He was discharged, at his own insistence, four weeks after admission. At that time the pulmonary component of the second heart sound was loud and he could walk less than 100 yards on the level.

Cardiac catheterisation was carried out eight weeks after the original admission; initially he had refused permission for invasive investigation. Despite intensive medical treatment his exercise tolerance remained very restricted. The loud pulmonary component of the second heart sound persisted and the pulmonary arterial pressure was found to be raised (60/28 mm Hg), as was left atrial pressure (mean 28 mm Hg). Systemic arterial pres-

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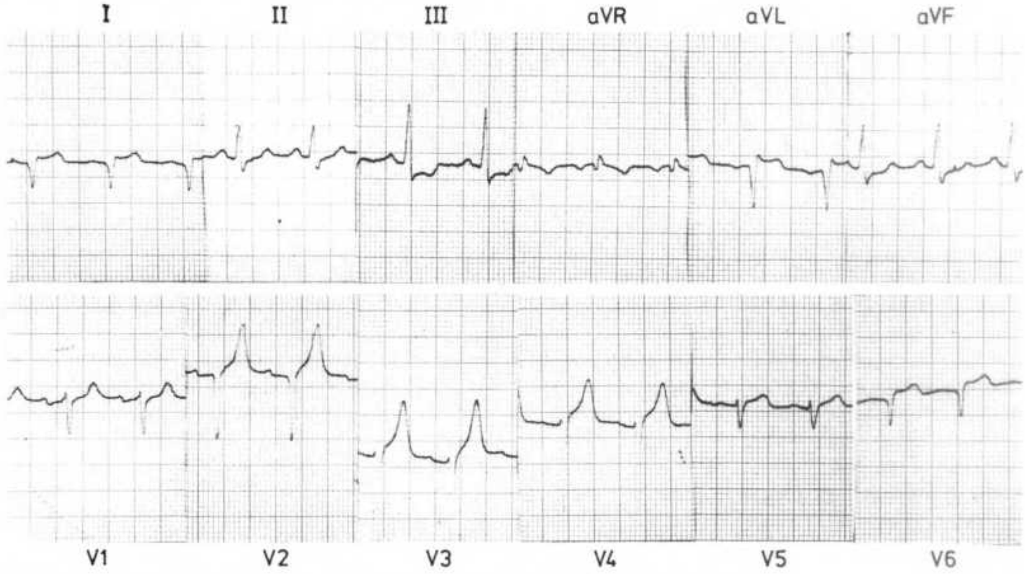

Fig. 1 *Electrocardiogram showing evidence of an anterolateral myocardial infarction.*

sure was 80/60 mm Hg. Left ventricular angiography demonstrated a considerably dilated ventricle, with widespread akinesis sparing only the septum and inferior wall. In the left coronary system there were several elongated stenoses, none of which appeared to be haemodynamically important. There was a stenosis of < 50% at the origin of the left anterior descending artery (Fig. 2). The dominant right coronary artery appeared to be normal.

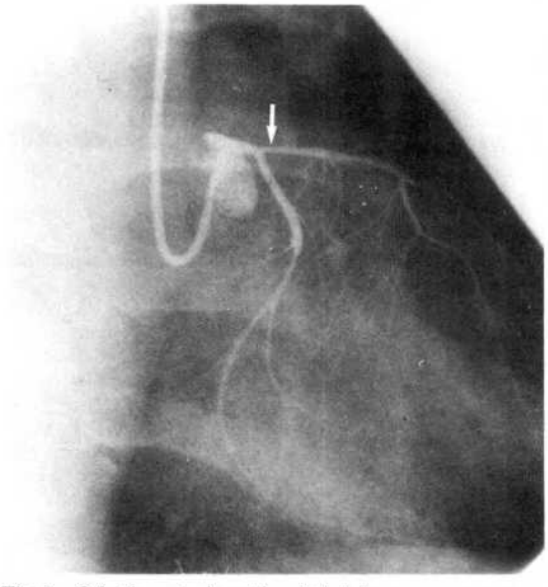

Fig. 2 *Selective arteriography of the left coronary artery showing slight proximal stenosis (arrow) of the left anterior descending coronary artery and an elongated stenosis in the mid-portion of the circumflex coronary artery.*

He was referred to Harefield Hospital for consideration for cardiac transplantation in view of the continuing cardiac failure and symptomatic disability secondary to the extensive left ventricular damage. Orthotopic cardiac transplantation was carried out three months after the myocardial infarction.

Pathological examination of the excised heart showed extensive fibrosis of the left ventricle, sparing only the inferior wall and part of the septum. The left main coronary artery and proximal left anterior descending artery were atheromatous.

Twelve months after transplantation the patient has resumed full time employment and is progressing well.

## Discussion

We are not aware of any other case report describing myocardial infarction after blunt chest trauma sustained while playing rugby football, nor do we know of any reported case in which myocardial infarction following blunt chest trauma of any cause has been treated by cardiac transplantation.

In cases of blunt chest trauma such as the one we describe it may be difficult to attribute with certainty the observed myocardial damage to the blow on the chest. In several cases only minutes passed between the time of the blow to the chest and the onset of cardiac ischaemic pain,[3 4] and so a causal relation seems likely. In others an hour or more elapsed between the chest trauma and the onset of symptoms[6] and in such cases the suggestion of a causal relation is less convincing. We believe that the short interval between the blow on the chest and the onset of typical symptoms of myocardial ischaemia in the case that we report strongly supports the interpretation that the chest trauma contributed to the onset of myocardial infarction.

The mechanism(s) of myocardial infarction after blunt chest trauma is unclear. Coronary artery dissection[2 7] and thrombosis[3 6] with or without recanalisation or focal spasm have been suggested as possible mechanisms. Thrombosis of a coronary artery after trauma has been shown at necropsy.[6 7] It remains to be established to what extent intimal dissection, plaque rupture, prolonged focal coronary spasm, or other mechanisms contribute to the onset of thrombosis. Recanalisation of an occluded artery may occur,[9] and so delay between trauma and coronary arteriography may falsely increase the number of cases with "normal" coronary arteries at angiography. In some cases myocardial contusion rather than coronary artery injury may have occurred. It appears likely that different mechanisms may operate in individual patients.

In our case we believe the most likely sequence of events was that thrombotic occlusion occurred at the origin of the left anterior descending artery after the blow on the chest and that recanalisation occurred before coronary arteriography was carried out. It may be that the blow on the chest caused fissuring of an atherosclerotic plaque and secondary thrombosis, similar to the "spontaneous" fissuring of plaques believed to occur frequently in ischaemic heart disease.[10]

Management of patients sustaining a myocardial infarction after blunt chest trauma must be empirical in view of the small number of reported cases. Initially it seems reasonable to manage the situation much as one would when myocardial infarction is secondary to coronary atheroma. Echocardiographic examination of the heart for other abnormalities secondary to trauma—for example haemopericardium—appears to be appropriate.

Many patients will make an uneventful recovery after their myocardial infarct but some may have residual angina pectoris.[4] This may be due to incorporation of mural thrombus into the coronary arterial wall which results in a haemodynamically important stenosis. It seems reasonable to treat such angina pectoris in the conventional manner.

Other patients may have cardiac failure which responds to medical treatment with diuretics, digoxin, and vasodilators (particularly the angiotensin converting enzyme inhibitors). In patients with severe left ventricular damage the quality of life may remain poor despite medical treatment,[11] and operation must be considered—for example, aneurysm resection[9]—if myocardial damage is localised. Unusually, left ventricular damage is severe, cardiac failure is refractory to intensive medical treatment, the quality of life is poor, and conventional surgery has little to offer. In these circumstances cardiac transplantation should be considered. The prognosis in our patient who had persistent cardiac failure, ventricular tachyarrhythmias, and recurrent pulmonary thromboembolism appeared to be poor. Cardiac transplantation has dramatically improved this patient's quality of life, and it appears likely to have improved his prognosis.

We are grateful to Mr M Yacoub, FRCS, for his invaluable help in the management of this case.

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*Br Heart J* 1986; **55**: 411–4

# Left coronary artery dissection: an unusual presentation

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*From the *Department of Pathology, Royal Brisbane Hospital, Herston; and the †Department of Pathology, University of Queensland, Australia*

SUMMARY Primary dissecting aneurysm of the left main stem coronary artery is a rare cause of coronary arterial occlusion that usually presents as sudden death or myocardial infarction in a young woman. A 32 year old woman with no signs of cardiac disease who died as the result of a right cerebral infarction was found to have coronary dissection and myocardial infarction at necropsy.

Dissection of a coronary artery may occur secondary to the extension of an aortic dissection, in association with coronary angiography,[1 2] or as a complication of cardiac operations.[3] Spontaneous primary dissection of a coronary artery is an uncommon cause of death that is seen predominantly in young women. It was first described in 1931 in the right coronary artery of a 42 year old woman.[4] Since then most case reports have shown that the dissection affects the anterior descending branch of the left coronary artery. Twelve cases of left main stem coronary artery involvement have been reported and in most of them dissection included the left anterior descending and/or left circumflex arteries as well.[5] Our case is unusual in that the dissection was restricted to the left main stem coronary artery and did not extend into either of its two branches.

## Case report

A white woman aged 32 had a history of asthma as a child. She had had three uneventful pregnancies; her youngest child was three years old. She was on no medication, was not taking oral contraceptives, and smoked up to 20 cigarettes a day.

One week before admission she and her family ate a meal of freshly caught prawns. Soon after this she experienced epigastric discomfort, vomiting, and diarrhoea; other members of the family were unaffected. Her illness persisted for two days and she attributed it to food poisoning. The temporal coincidence of these symptoms with the age of the dissection, however, suggests that they may have been produced by vagal or sympathetic stimulation caused by the dissection. After this episode she remained well for four days. On the day of admission she noted the sudden onset of paraesthesia and weakness on the left side of her body after she had eaten her evening meal. She was transferred to the casualty department of the Royal Brisbane Hospital where she was found to be conscious but drowsy. Blood pressure was 80/60 mm Hg. Physical examination showed a left sided decrease in muscle tone and loss of muscle power associated with hyperreflexia. The remainder of the examination was unremarkable. In particular the pulse rate was 72 beats per minute and regular, the heart sounds were normal, and no murmurs were heard.

Investigations showed widespread depression of the ST segment in leads II, III, and aVF on electrocardiography (Fig. 1). The only biochemical abnormality detected was a lactate dehydrogenase activity of 542 units/litre (normal range 125–220). Chest and skull *x* rays were reported to show no abnormality. A computerised axial tomography head scan showed a right sided low density lesion that was consistent with a large infarct in the area of distribution of the right middle cerebral artery. There was no evidence of subarachnoid haemorrhage. No underlying cause was found for the right cerebral infarct. Her neurological state deteriorated and she died two days after admission.

Requests for reprints to Dr R H Steele, Department of Pathology, University of Queensland, Herston Road, Herston, Queensland 4006, Australia

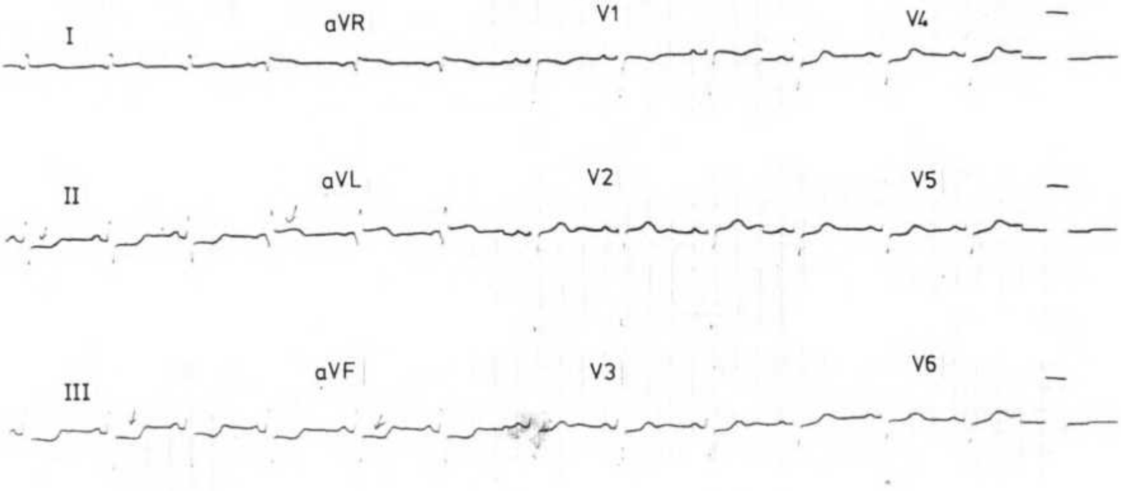

Fig. 1 *Electrocardiogram obtained at admission one week after first symptoms. It was not considered to be diagnostic of heart disease.*

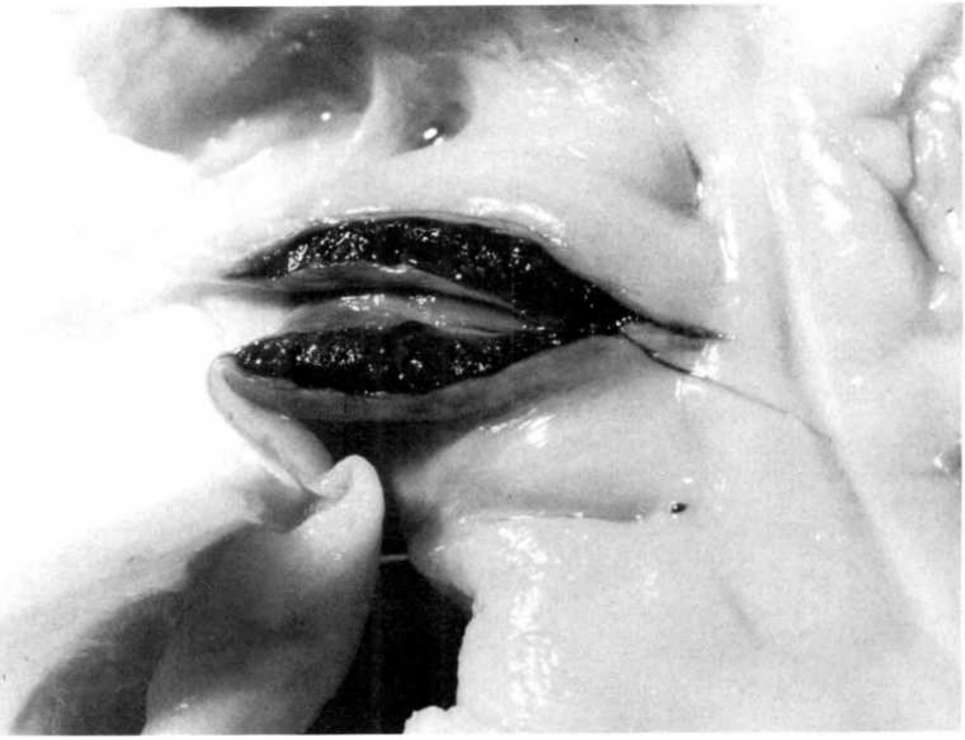

Fig. 2 *The first part of the left coronary artery opened to show the dissecting aneurysm.*

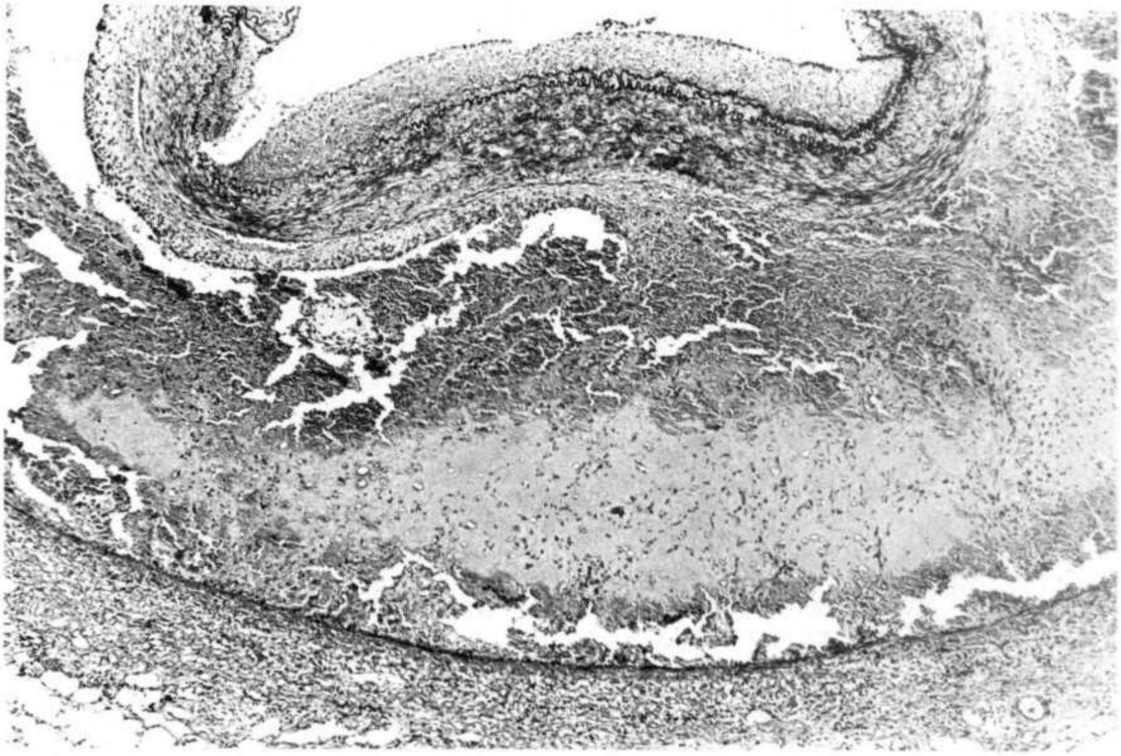

Fig. 3 *Photomicrograph of wall of the left coronary artery showing the dissection in the outer third of the media. Verhoff van Gieson; original magnification × 20.*

## Pathology

External examination at necropsy showed the body of a young adult female (height 1·65 m, weight 68 kg). Her fingers were unusually long when compared with her body build and gave the subjective impression of arachnodactyly. No other features suggestive of Marfan's syndrome were found, although they were specifically sought. The heart was of normal size and weighed 320 g. Subendocardial to full thickness infarction affected the anterior one third of the interventricular septum and the anterior and lateral portions of the free wall of the left ventricle. The region infarcted was in the distribution area of the left coronary artery. The coronary arteries arose normally from the aorta and had a normal anatomical distribution with the left main stem coronary artery bifurcating and giving rise to normally sized left anterior descending and left circumflex branches.

There was a dissecting aneurysm of the left main stem artery (Fig. 2) which had resulted in total occlusion of the vessel lumen. This dissection affected the length of the left main stem but did not involve the aorta or either of the two branches of the left coronary artery. No internal tear was identified.

Examination of the remainder of the heart showed mural thrombi in the left atrial appendage and in the left ventricle overlying the area of infarction. The right coronary artery, aorta, and its branches and large muscular arteries throughout the body appeared to be macroscopically normal. An occlusive thrombus, consistent with an embolus from the left atrium or ventricular wall, was found in the distal right internal carotid artery and there was recent infarction of the right cerebral hemisphere in the area of distribution of the right middle cerebral artery.

Histological examination showed a circumferential dissection of the left main stem coronary artery with separation of the outer one third of the media from the adventitia and evidence of early organisation of the clotted blood (Fig. 3). There were a few lymphocytes and eosinophils in the adventitia, but there was no evidence of vasculitis. Diffuse intimal thickening with abundant smooth muscle cells and some elastin was seen in the left main stem coronary artery, but there were no features of atherosclerosis and no evidence of intimal disruption.

Similar changes were noted in the proximal portions of the right coronary artery. The arterial media of both vessels contained recognisable small pools of Alcian blue positive mucopolysaccharide material. Examination of the ascending and descending portions of the thoracic aorta showed prominent accumulations of mucopolysaccharide within the lamellar units and this was associated with fragmentation and focal loss of elastic fibres. No evidence of dissection was found in the root of the aorta adjacent to the left coronary ostium.

## Discussion

Spontaneous dissection of a coronary artery unrelated to coronary angiography, cardiac surgery, and blunt chest trauma is rare but well recognised. At least 75 cases have been reported since the original description in 1931,[5] and several reviews of the published cases have demonstrated similar background features.[5 6] Most patients are women (60 of 75), most are young (mean age 37–42 years), and 19 of 60 cases reported in women occurred peripartum. Apart from this association with pregnancy and the puerperium, coronary artery dissection is usually not associated with any other clinical condition or pre-existing disease state. One case has been previously reported in association with arachnodactyly. Though, as in our case, the patient had no other stigmata of Marfan's syndrome.[7] In most cases the left anterior descending coronary artery is dissected but any of the main coronary arteries may be affected. Twelve cases of dissection of the left main stem coronary artery have been reported.[5] Many of the cases have shown extension of the dissection into the left anterior descending and or left circumflex branches but this feature was not present in our case.

Clinically most cases present with sudden death or with symptoms and signs of myocardial infarction. Our case is unusual in that the probable episode of dissection was believed by the patient to be a bout of food poisoning and she did not seek medical assistance. She then remained well and symptom free for four days until she presentated with an acute cerebral infarct, presumably the result of embolus from the left ventricle. Even on admission there was no clinical sign of heart disease and the electrocardiographic changes were regarded as not specific.

The histological changes in the coronary arteries and aorta are of interest. Cystic medial necrosis (the pooling of acid mucopolysaccharide material) has been described in 25 of the 66 cases of spontaneous dissection examined microscopically. These included a woman in the post partum period,[8] a woman who had not recently been pregnant,[9] and an elderly man with alcoholic liver disease.[10] As pointed out by Glasgow *et al* in many cases in both men and women there is no evidence of cystic medial necrosis, even when the aorta and coronary arteries are carefully examined.[5] In our case, however, Alcian blue positive material was found in the media of the left main stem coronary artery as well as in the media of the proximal right coronary artery and the aorta. Fragmentation and loss of elastin was an associated feature in the aorta. The association of cystic medial necrosis in both coronary artery and proximal aorta has been mentioned in some of the previously reported cases,[10 11] though not in others.

Molloy *et al* and Malloch have emphasised that dissection should be suspected in young women with no previous history who present with unexpected circulatory collapse, myocardial ischaemia, or infarction, especially in the puerperium.[9 12] Suspicion of the diagnosis may then lead to emergency investigation of the coronary arteries and possible life-saving cardiac operation. Unfortunately our patient had no definite symptoms or signs to indicate a cardiac disease and, as with so many previously reported cases, the diagnosis was made at necropsy.

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*Br Heart J* 1986; 55: 415–7

# Ductus arteriosus associated with an anomalous left coronary artery arising from the pulmonary artery: catastrophe after duct ligation

EDGARDO ORTIZ, MARC DE LEVAL, JANE SOMERVILLE

*From the Paediatric and Adolescent Unit, National Heart Hospital, and the Hospital for Sick Children, Great Ormond Street, London*

SUMMARY Chronic left ventricular failure developed two months after ligation of an apparently uncomplicated large ductus arteriosus in a one year old girl. Two years later deterioration had progressed to a terminal stage. An anomalous left coronary artery arising from the pulmonary artery had not been recognised before duct ligation. This anomaly was diagnosed two years after ligation and was then treated by surgical redirection, but the patient died of severe left ventricular dysfunction.

The association of ductus arteriosus with an anomalous left coronary artery from the pulmonary artery has been reported once before.[1] Recognition of the coronary anomaly before ligation of a large duct is difficult and the effect of routine ligation may be disastrous. We describe a patient with these associated lesions in whom the coronary abnormality was not diagnosed until two years after ligation. Despite surgical redirection of the anomalous artery she died.

## Case report

A one year old girl from Oman was referred in chronic heart failure with signs of a large left to right shunt and collapsing pulses. She was a fullterm uncomplicated delivery (birth weight 3·5 kg) and had developed heart failure at seven weeks. On admission she had signs of ductus arteriosus together with an apical pansystolic murmur suggestive of mitral regurgitation.

The chest *x* ray showed cardiomegaly and plethora, and the electrocardiogram showed normal axis, P mitrale, left ventricular hypertrophy with deep S in V4R and V1, and deep but narrow q waves preceding tall R waves in V5 and V6 with normal upright T waves.

Cross sectional echocardiography confirmed the large duct, a dilated but well contracting left ventricle, enlarged left atrium, a bicuspid aortic valve, and abnormal movement of the posterior mitral valve leaflet, which was attributed to papillary muscle dysfunction and ventricular dilatation.

The duct was ligated and her recovery was uneventful in the first week. A late systolic murmur persisted at the apex. The postoperative echocardiogram confirmed the same posterior mitral leaflet abnormality. The left ventricular cavity was smaller than before ligation; no comment was made on its function.

She returned to Oman on the eighth postoperative day. There was no further information until the consultant paediatrician sought the opinion of JS two years later. Apparently, the child had become unwell two months after her return home and since then she had suffered from congestive heart failure.

She had features of left-sided heart failure and chronic collapse of the left lung due to pressure on the left main bronchus from cardiomegaly. There were no murmurs, but the third heart sound was loud and the peripheral pulses were reduced. A possible explanation for the deterioration was the presence of an anomalous left coronary artery from the pulmonary artery. On advice she had been returned to the UK for investigation to exclude this.

On admission the electrocardiogram showed sinus rhythm, left axis deviation, smaller qR pattern with upright T waves, smaller R waves than before, and slightly depressed ST segments that were not diag-

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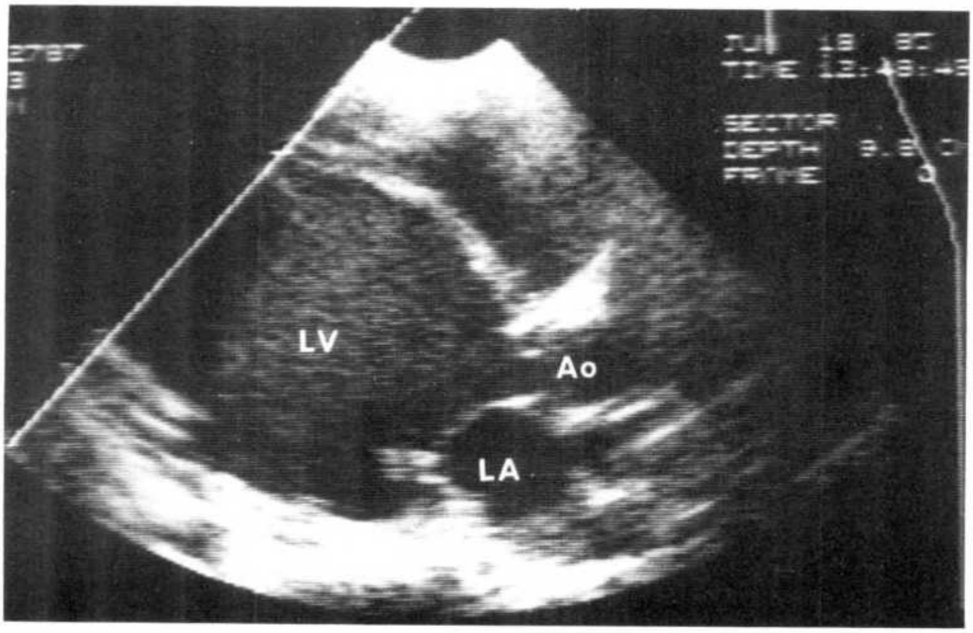

Fig. 1 *Cross sectional echocardiogram in the parasternal long axis view at left sternal border showing the dilated left ventricular cavity and the thin interventricular septum and posterior wall of the left ventricle. Impaired ventricular function and poor movement of the mitral valve were demonstrated on real time. Ao, aorta; LA, left atrium; LV, left ventricle.*

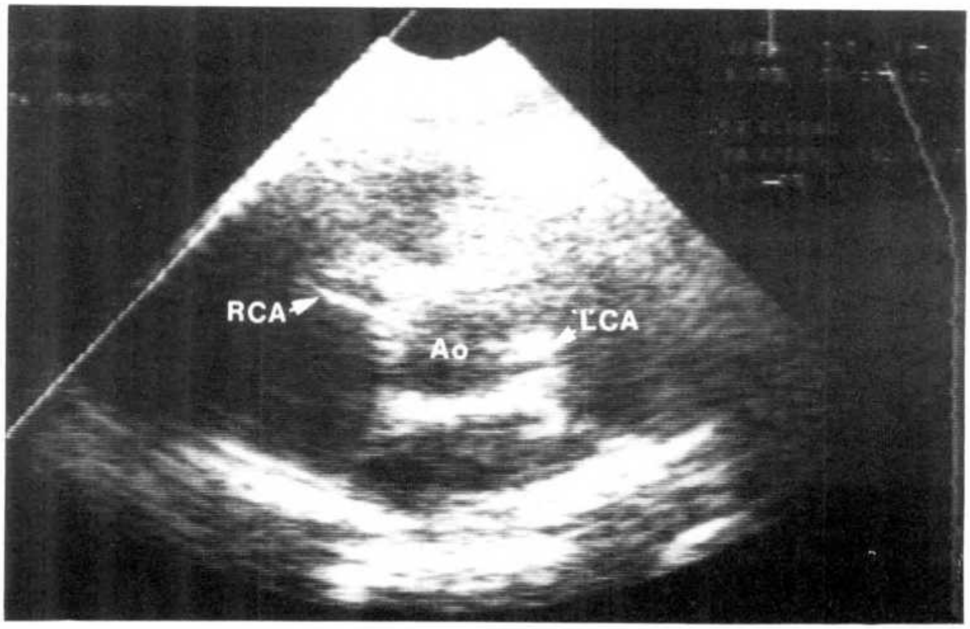

Fig. 2 *Cross sectional echocardiogram in the parasternal short axis view showing the prominent right coronary artery and the "left" coronary artery originating from the aortic sinus. Ao, aorta; "L"CA, "left" coronary atery; RCA, right coronary artery.*

nostic of infarction or ischaemia. Cross sectional echocardiography showed a dilated thin walled and poorly contracting left ventricle; these features were particularly pronounced in the anterior portion. The left atrium was enlarged and there was poor but symmetrical movement of the mitral cusps (Fig. 1) The coronary arteries appeared to emerge normally from the aorta (Fig. 2).

Cardiac catheterisation confirmed poor left ventricular function, with an ejection fraction of about 10% and end diastolic pressure of 20 mm Hg; the aortogram showed the large right coronary artery retrogradely perfusing the left coronary artery that entered the pulmonary artery posteriorly; the left anterior descending branch was not clearly seen.

Despite the high risk, because of poor ventricular function, we hoped that ligation or reimplantation of the left coronary artery might improve left ventricular function. After cardiac catheterisation she was intubated and ventilated, and treated with inotropes for 48 hours before operation. We had planned to ligate the left coronary artery but at operation we found two coronary orifices in the posterior sinus of the pulmonary artery which made this difficult. With cardiopulmonary bypass and cooling the left coronary orifices were directed to the aorta by means of a created aortopulmonary window and pericardial tunnel. The patient had difficulty coming off the bypass and when this was finally achieved the heart could not maintain coronary flow in diastole.

## Discussion

When the left coronary artery originates from the pulmonary artery, the left ventricle is perfused with venous blood. Unless there is an increase in pulmonary diastolic pressure, there can be little or no perfusion from the pulmonary artery. In the fetus with an open duct and raised pulmonary vascular resistance, perfusion of the left ventricle is adequate for normal development. In the postnatal period, when the pulmonary vascular resistance falls and the duct closes, the perfusion of the left ventricle suffers and the effects of this are manifested weeks, months, and sometimes years later as ischaemic cardiomyopathy, cardiac infarction, left ventricular aneurysm, or mitral regurgitation.

If a large duct persists with hyperkinetic pulmonary hypertension, the left coronary artery will be perfused with oxygenated blood. The adequacy of perfusion will depend upon the degree to which pulmonary vascular resistance is increased. In our patient this probably was not high since although left ventricular function was slightly compromised there was no major infarction. Perhaps impaired left ventricular function contributed to papillary muscle dysfunction and hence mitral regurgitation. Duct closure produced an acute change in pulmonary artery pressure, flow, and oxygen saturation to the left coronary artery. Indeed in some cases it could be a cause of sudden deterioration or cardiac arrest after duct ligation. There was no sudden deterioration in our patient, however, presumably because the child was one year old at duct ligation and intercoronary collaterals had already developed to maintain left ventricular myocardial perfusion. This was inadequate for myocardial performance during normal active life.

Retrospective review of the postoperative echocardiogram showed definite evidence of impaired left ventricular contraction seven days after duct ligation. Left heart failure developed two months later due to ischaemic myopathy. By the time the condition was recognised the extensive myocardial damage was irreversible. If attention had been given to the deterioration in left ventricular function in the first postoperative week, earlier operation for the anomalous left coronary artery might have prevented the damage.

What measures may be taken to avoid missing the rare diagnosis of an anomalous coronary artery in the presence of a sizeable duct for which ligation (closure) is indicated? Normally no invasive investigation is done in patients with a ductus arteriosus, and even when catheterisation is performed, aortography is unlikely to show the anomalous coronary artery anatomy. The clinical and electrocardiographic features that are suggestive of an atypical duct were not present in this patient. Perhaps the early development of congestive heart failure in a fullterm baby with a patent duct and presence of mitral regurgitation with no demonstrable cusp abnormality should have suggested something unusual. Certainly the demonstration of decreased left ventricular function after duct ligation should have prompted early reinvestigation and a search for a coronary abnormality.

We have found that echocardiography is unreliable for the diagnosis of an anomalous coronary artery in infants and children because of the narrow separation between the transverse sinus of the pericardium and the left coronary artery as they pass behind the pulmonary trunk, a finding confirmed by others.[2] When the appearance of the origins of the coronary arteries is unusual, selective angiography is indicated.

EO is a Squibb Medical Research Systems Fellow.

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*Br Heart J* 1986; **55:** 418–20

# *Correspondence*

## The challenge and the reproach of infective endocarditis

Sir,
We have the following comments to make on Professor Goodwin's editorial (*Br Heart J* 1985; **54:** 115–8).

(*a*) We know of no evidence that fungal endocarditis has increased, and certainly not as the result of "intensive and lengthy therapy for advanced bacterial infective endocarditis." We therefore do not agree with the recommendation for weekly prophylactic amphotericin. Nor do we know of any evidence that the immunocompromised are especially vulnerable to endocarditis.

(*b*) It is not known whether appropriate prophylaxis will prevent endocarditis although it is assumed that many potential cases are prevented by it.

(*c*) The recommendation of the British Society for Antimicrobial Chemotherapy Working Party is for a single oral dose of 3 g not 2 g of amoxycillin for dental prophylaxis.

(*d*) Not all "streptococci likely to have come from the mouth" can be satisfactorily killed in vitro with penicillin alone. Thus treatment with penicillin alone is inappropriate, as indeed is ampicillin alone for faecal streptococci.

(*e*) Potassium penicillin in large intravenous doses can cause hyperkalaemia, but it is no longer available for parenteral use.

(*f*) The recommendations for gentamicin blood concentrations in streptococcal endocarditis might result in toxicity. The working party recommended that gentamicin should be given in a low dose to enchance the activity of penicillin. Peak blood concentrations of 3–5 mg/l and trough blood concentrations $< 1$ mg/l are sufficient for this purpose. Gentamicin should seldom be given for more than two weeks. Gentamicin can be used in combination with flucloxacillin to treat staphylococcal endocarditis and here the dose will need to be greater than that for streptococcal infection to achieve peak blood concentrations of 5–10 mg/l and trough blood concentrations of $< 2$ mg/l.

(*g*) Early prosthetic endocarditis with *Staphylococcus aureus* is nearly always the result of sternal wound infection and resultant bacteraemia. The aetiology of late prosthetic endocarditis is quite different from early onset infection. It is caused by the same spectrum of organisms as those causing natural valve infection.

(*h*) Antibiotic resistance of the infecting organism is seldom the reason for a fatal outcome in endocarditis. The mortality of this disease remains high because of late diagnosis, poor choice and incorrect dosage of antibiotics, and, more important, late referral to cardiologists and cardiac surgeons.

(*i*) The most important initial investigations in suspected endocarditis are blood cultures. An erythrocyte sedimentation rate and haemoglobin are not a substitute because they are non-specific. Where "viridans streptococci" are cultured from the blood the diagnosis is nearly always endocarditis and sometimes it may come as a surprise.

Susannah Eykyn
on behalf of the working party on Endocarditis of
the British Society for Antimicrobial Chemotherapy

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This letter was shown to Professor Goodwin, who replies as follows:

Sir,
I welcome the opportunity of replying to Dr Eykyn's important comments as her letter gives me the chance to reinforce the message in my editorial that early diagnosis and early consultation with the cardiac surgeons are important for success in treatment and reduction of mortality.

(*a*) I know of no evidence that fungal infection has increased nor did I quote any. I suggested that "fungal infection may paradoxically have increased as a result of more intensive and lengthy chemotherapy for advanced bacterial infective endocarditis." This is a personal view based on personal experience, and I believe this view may be shared by others.[1]

I pointed out that "patients who are immunologically compromised, such as those taking immunosuppressive drugs are especially vulnerable to infection of any sort." I do not think that any experienced clinician or microbiologist would seriously challenge this statement. I did not quote any evidence that such patients were especially vulnerable to infective endocarditis, though it seems reasonable to suppose that they might be.[2] Immunosuppressed patients are listed among those specially vulnerable to infective endocarditis in the latest report of the Royal College of Physicians of London Research Unit.[3]

(*b*) I agree that it is assumed that many potential cases of infective endocarditis are prevented by appropriate prophylaxis, and I pointed out that "Although prophylaxis remains a somewhat imprecise exercise, it should at least be meticulously applied to patients who are especially at risk."

(*c*) The dose of 2 g of amoxycillin by mouth one hour before dental work for outpatients was an error for which I make due apology. The correct dose as recommended by the working party of the British Society for Antimicrobial Chemotherapy[4] is indeed a single dose of 3 g. It is of interest though, that Shanson *et al* in 1978[5] showed that a single dose of 2 g amoxycillin given one hour before tooth extraction reduced the incidence of bacteraemia detected from 14 of 14 controls to two out of 14 given amoxycillin, and a single 2 g dose was advised by Oakley in 1979.[6] Two years later, Shanson *et al* reported that 3 g of amoxycillin effectively prevented bacteraemia after dental extraction.[7]

(*d*) I entirely agree that penicillin alone is not appropriate for treatment of streptococcal or staphylococcal endocarditis, as I wrote under the heading of Treatment: "Since over 80% of infections are due to staphylococci or streptococci, initial treatment should be with a combination of drugs, such as gentamicin and penicillin." I did not suggest that ampicillin alone should be given for faecal streptococcal infections.

(*e*) I am grateful to Dr Eykyn for emphasising that potassium penicillin is not available for parenteral use.

(*f*) The gentamicin blood levels that I advocated, based on personal experience and published recommendations,[8] are indeed somewhat different from those quoted by Dr Eykyn—that is peak blood concentrations of 3–5 mg/l and trough concentrations of < 1 mg/l. I said that peak concentrations should not exceed 14 mg/l or fall below 5 mg/l and trough concentrations should not exceed 2 mg/l. The Guide to Antimicrobial Therapy published by the Use of Drugs Subcommittee of the Ealing, Hounslow and North Hammersmith District in 1981 states that the gentamicin nomogram of Mawer *et al*[9] is designed to give serum concentrations of gentamicin within the range 3–10 mg/l two hours after each intramuscular dose.

(*g*) I do not agree that early prosthetic staphylococcal endocarditis is "nearly always" the result of sternal wound infection. Certainly the sternal wound may be the source of the infection, but entry of staphylococci from the patient's skin when the drains are removed is important.

(*h*) I wrote that "reasons for the failure (to reduce mortality) are multiple and include organisms resistant to antibiotics"... I agree that this is not the most frequent reason for failure and I mentioned other causes including more direct exposure of the heart to infection by open operation, insertion of foreign bodies into the heart, and older and sicker patients who develop the disease. I agree entirely that the high mortality of infective endocarditis is due mainly to delay in diagnosis, and late referral to cardiologists and cardiac surgeons as I stated clearly in the editorial. The use of incorrect doses of antibiotics is a less common though not an unimportant reason.

(*i*) Of course the most important investigation is blood culture. But a high erythrocyte sedimentation rate though it is not specific can be a very useful warning to investigate further in a suggestive clinical situation. The test is simpler and gives an earlier result than blood culture. I agree that streptococci of the viridans group in the blood nearly always indicate endocarditis, but the diagnosis rarely comes "as a surprise" to experienced cardiologists and clinicians.

I make no apology for quoting personal views and experience, because I feel that it is the function of an editorial to express these and provoke lively discussion.

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# Myocarditis confirmed by biopsy presenting as acute myocardial infarction

Sir,

We were very interested to read the report by Costanzo-Nordin *et al* in the January 1985 issue of the *British Heart Journal* of two cases of myocarditis confirmed by biopsy which presented as acute myocardial infarction.[1]

In April 1984 we reported on two similar cases in *Archives des Maladies du Coeur*.[2] These occurred in a 31 year old woman and a 37 year old man who were referred to our intensive care unit with the diagnosis of acute anterior myocardial infarction. In both cases acute cardiogenic shock with diastolic equalisation of pressure lead us to the incorrect diagnosis of heart rupture. But in both cases cardiac catheterisation showed normal coronary arteries, and the acute myocarditis that we diagnosed healed without any sequelae (normal electrocardiogram, echocardiography, and angiography). In the male patient the diagnosis was based on serological investigation which showed a high and increasing titre of *Chlamydia trachomatis*. We recognise that cardiac biopsy cannot be performed during the subacute stage of the disease, but we agree with Costanzo-Nordin *et al* that biopsy may be useful in identifying myocarditis that is associated with or simulates acute myocardial infarction.

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# *Notices*

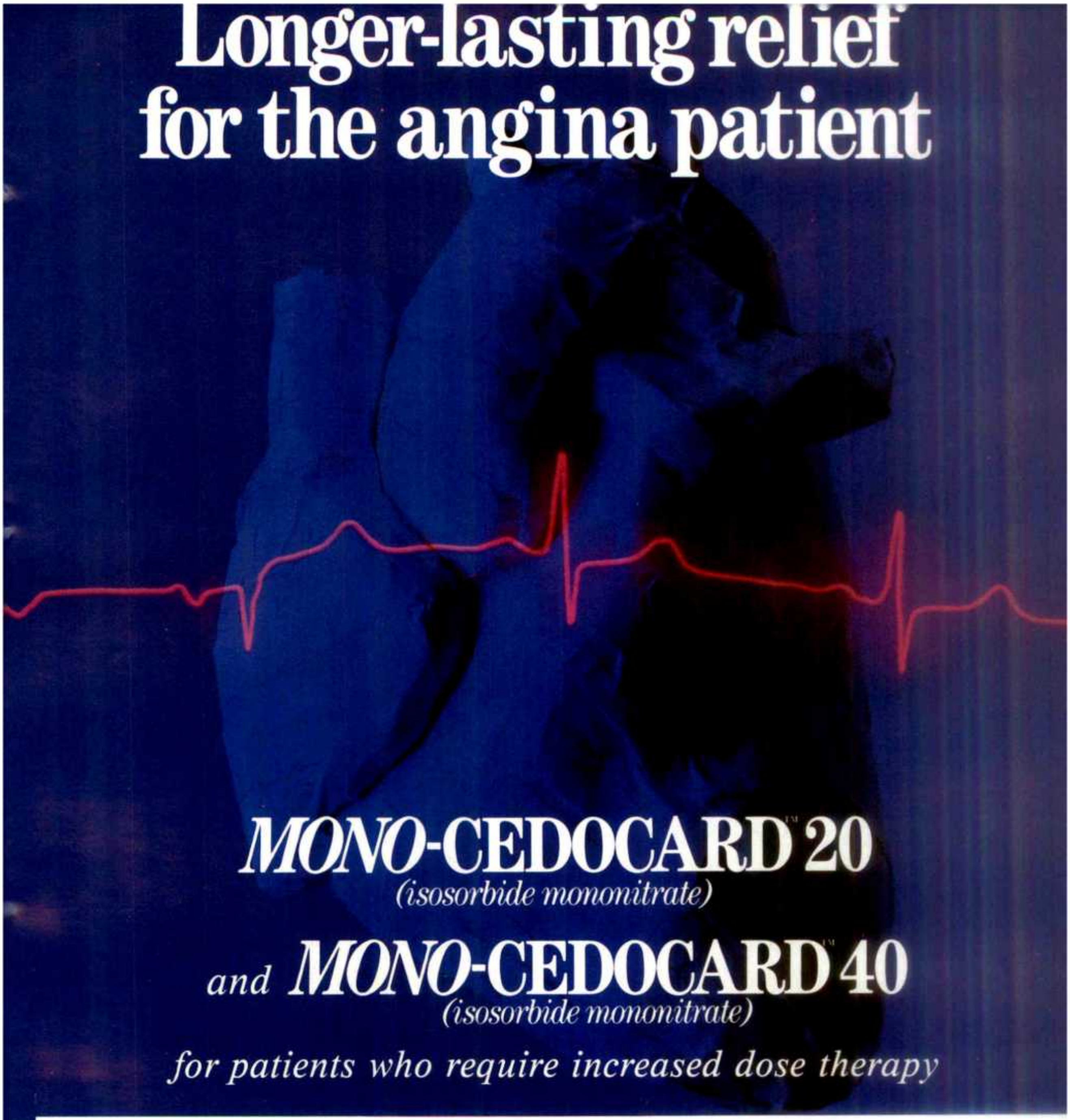
## British Cardiac Society

The Annual General Meeting for 1986 will take place in York on 2 and 3 April 1986, and the closing date for receipt of abstracts was 2 January 1986.

The Autumn Meeting will be held at the Wembley Conference Centre, London, on 25 to 27 November 1986, and the closing date for receipt of abstracts will be 1 August 1986.

## Peter Debye prize

The University of Limburg will award the 1987 Peter Debye prize in cardiovascular diseases. The prize of 20 000 guilders has been provided by the Edmond Hustinx Foundation. Further information from: Dr E H S Drenthe, Secretary of the Jury, University of Limburg, Office of the Rector, PO Box 616, 6200 MD Maastricht, The Netherlands.



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*Warnings/Precautions:* Consumption of alcohol should be avoided during treatment, as reaction [illegible]

*Adverse effects:* Generally, no serious effects are to be expected. Headache, dizziness, fatigue, palpitations, orthostatic hypotension and flushing may occur, especially at the beginning of treatment. These reactions can usually be controlled by a temporary dosage reduction.

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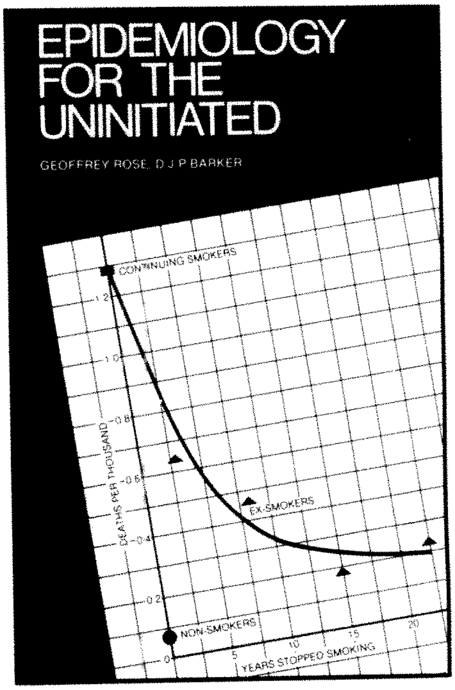

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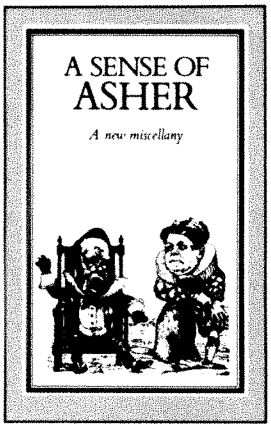

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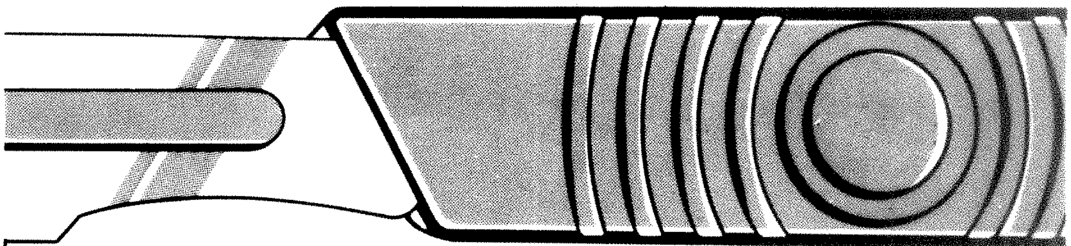

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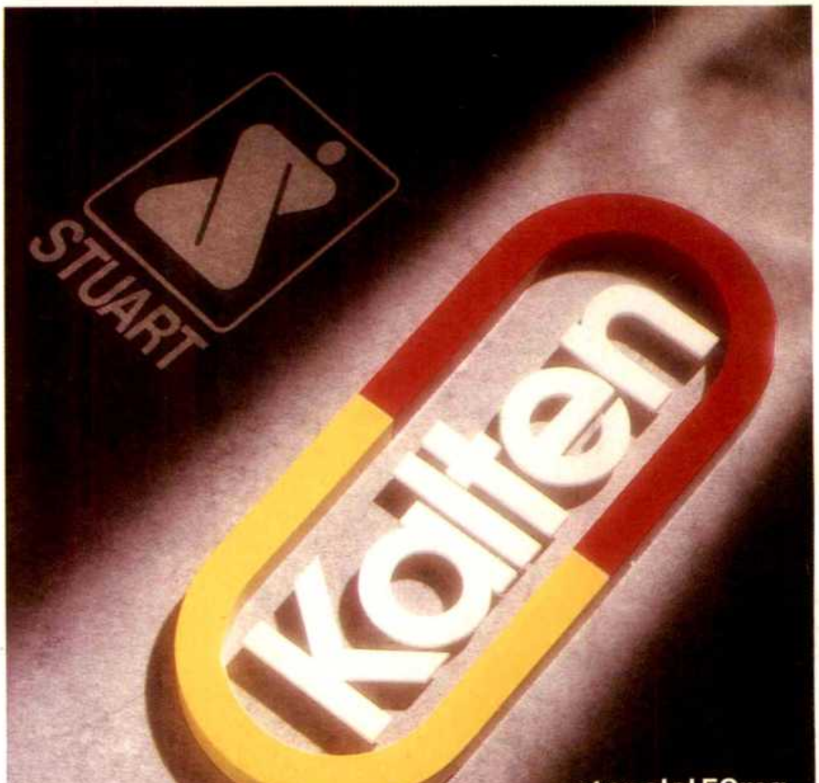

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May 1986 Vol 55 No 5

25.7.87

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*A monthly journal of cardiology published in association with the British Cardiac Society*

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ASTM CODEN: BHJUAV 55(5) 421—530 (1986)
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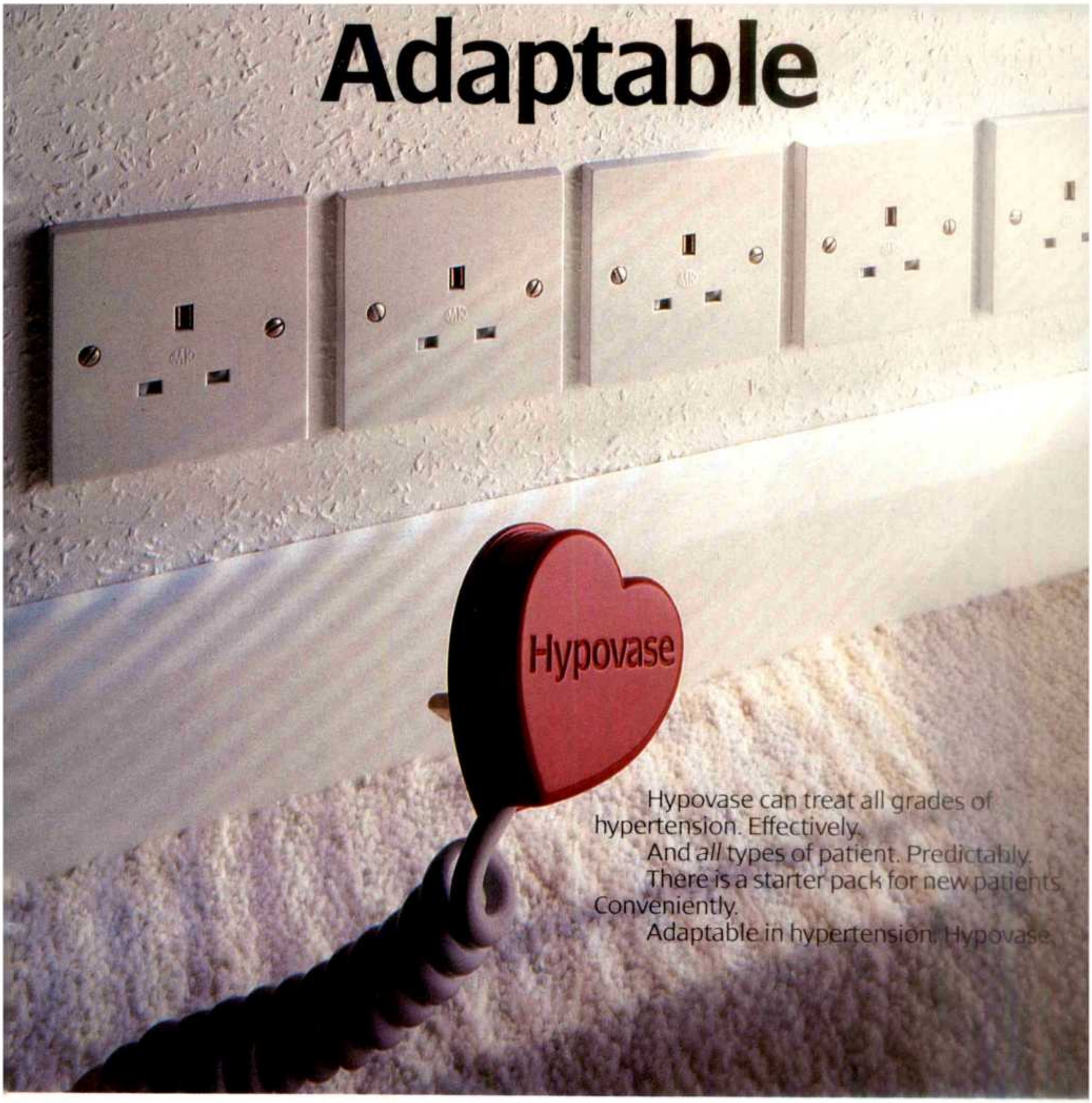

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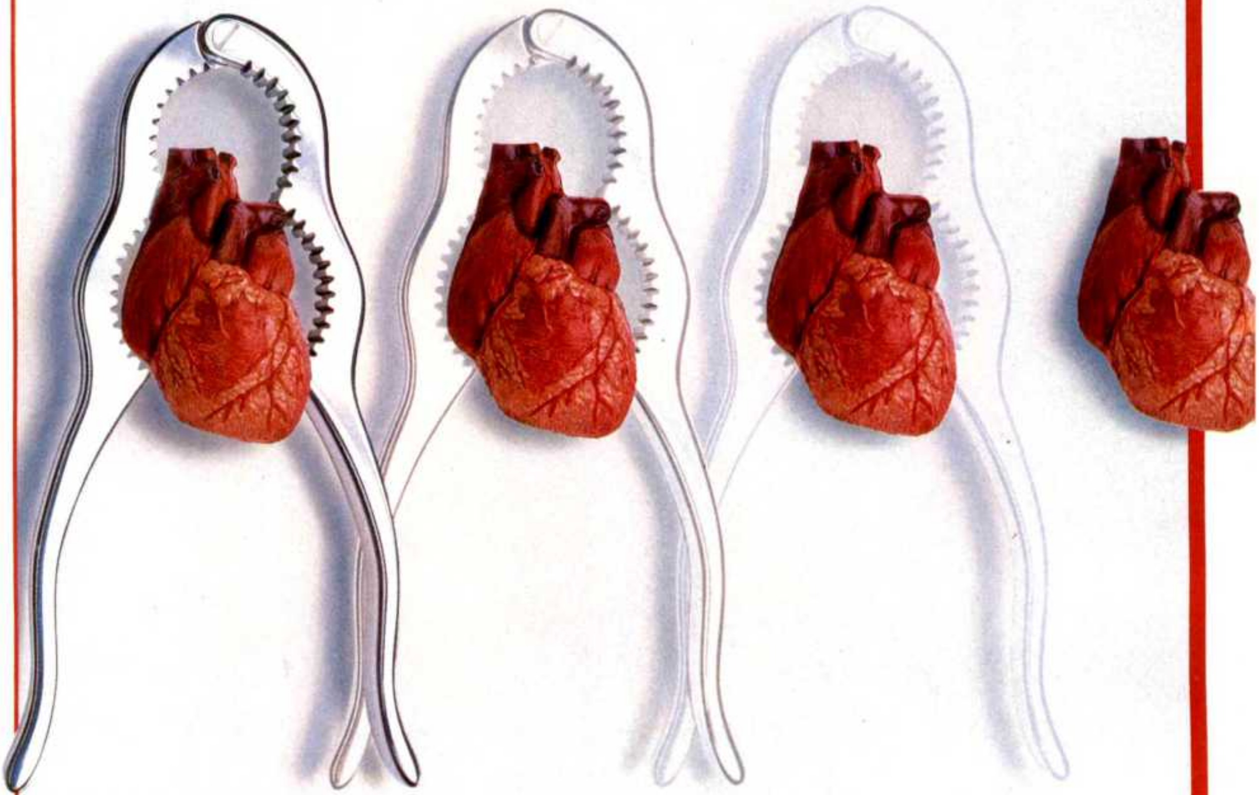

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*Br Heart J* 1986; **55:** 421–2

# *Editorial*

# Radiation hazards for cardiologists

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At its March 1985 meeting in Paris[1] the International Commission on Radiation Protection (ICRP) heavily reinforced the recommendation that the maximum permissible dose of radiation to the lens of the eye should be 150 mSv per year of working life.[2] Is this of relevance to interventional cardiologists and what should they do about it?

In correctly set up apparatus and when the operator is wearing the standard effective (that is undamaged) protective lead apron the chief hazard to interventional cardiologists and radiologists is radiation damage to the lens of the eye leading to cataracts.[2] Are critical eye dose levels likely to be reached in interventional cardiologists? The answer is not clear, particularly with modern multiangulated *x* ray apparatus and with modern techniques such as coronary angioplasty and pacing.

In 1978 Balter *et al* studied the radiation dose to operators during coronary arteriography using modern multiangulated apparatus and performed from the arm.[3] The eyes were considered to be the organs most at risk receiving 0·06 mSv without the use of additional shielding and 0·019 mSv with the special shields during angiographic examination. This group concluded that an operator could perform 29 examinations per week (mean fluoroscopy 12·7 min and mean cine radiography 110 s) without reaching the ICRP threshold for non-designated workers (that is those who are unlikely to exceed 30% of the maximum permissible dose).

Since 1978 pacemaker implants and coronary angioplasty, with their long screening times, have become more widespread and a recent paper,[4] combined with the ICRP reassertion of the maximum permissible dose to the eye, has revived the issue of what is a safe workload for the interventional cardiologist.

Jeans *et al* measured isodose curves produced from a modern multiangulated set and a water phantom, and used the curves to calculate dose rates for staff present in the *x* ray room during various cardiac interventional procedures.[4] This phantom neglects the effect on scattered radiation production and distribution of the large air volume in the lungs. The paper also makes use of a "weighted surface dose" which is not an ICRP concept. Jeans *et al* concluded that interventional cardiologists doing 200 cardiac catheterisations, one or two angioplasties, and 30 pacemaker implants in a year would remain within safe exposure limits. The addition of five further angioplasties, electrophysiological studies, or the use of more complex catheter ablation techniques on arrhythmia patients would increase the average dose that interventional cardiologists would receive to three tenths of the maximum permissible eye dose. When they measured actual dose levels, however, they found that these were only about one third of those calculated from the phantom study.

These measured values accord fairly well with those published by Dash and Leaman in 1984 which were made on a rotating cradle rather than on a dedicated multiangle tube support system.[5] These workers found eye lens doses of 0·175 mSv per angioplasty procedure and rather lower 0·075 mSv per angiogram. This suggests that a single operator could perform over 650 coronary angiographic examinations or 285 angioplasty procedures per year before reaching the 50 mSv limit of eye dose. Dash and Leaman found that lead glasses reduce the eye dose by a factor of 35%. Similar conclusions were obtained from the measurements by Balter *et al.*[3]

Under the new regulations[6] any worker who is likely to exceed 30% of the maximum permissible dose is classified as a designated worker. Such workers must be rigorously monitored. If there is any possibility of their exceeding the maximum permissible dose they should be stopped; and they may be restrained by law.

Should all those who perform coronary angioplasty as well as other catheterisation procedures automatically become designated workers? Probably not, but in view of the three fold difference between the conclusions of Balter *et al*[3] and those of Jeans *et al*[4] doses of radiation to the eyes should be measured in more at risk workers. The local radiation protection advisor should measure doses in all staff who are likely to be affected, since local variations in approach and practice may be major determinants of

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safety.

The ICRP also drew attention to reported examples of practices causing concern. These included the performance of complex radiological procedures by physicians or surgeons without training in radiology and radiation protection. Some operators may feel that the needs of the patient outweigh a future risk of radiation injury to themselves, and on occasion individuals have removed monitoring devices to avoid the identification of high dose levels.[1] Such actions will be illegal in a designated worker.

Until the magnitude of the problem is known cardiologists should use the following simple measures to minimise radiation dosage to themselves.

Those performing catheterisations should be instructed in radiation safety practice before or early in their training. Simple guidelines and an understanding of the main source of irradiation to the operator should help to improve practice.

There are two sources of radiation to the operator—the main beam and radiation scatter from the main beam as it traverses the patient. The operator must never get any part of his or her body in the main beam where dose is highest. The lead shutters on the *x* ray tube should be used to produce the smallest aperture necessary to perform the procedure. This is because the dosage to the patient and the scatter to the staff increase with the increase of area of patient irradiated. A small aperture also improves the quality of the image, which is degraded by scatter. Proper maintenance of the apparatus and quality control will also reduce radiation to both staff and patients.

Screening and cineradiography times should be kept as short as possible, and if possible the cine framing rate should be reduced (25 frames per second is usually adequate). The operator dose is markedly attenuated by distance, so it is worth while taking a step backwards away from the patient during cineradiography, because doses to the patient and operator during cineradiography are twenty times higher than during fluoroscopy.[3]

A projection which minimises scatter to the operator should be chosen. Scatter is mostly back scatter and is increased when the *x* ray tube is placed between the patient and the operator,[4] rather than beyond the patient. Lead aprons (0·35 mm lead equivalent), which should always be worn, reduce the trunk dose by a factor of approximately 15.

Operators who perform angioplasties may need to protect their eyes with a shield or spectacles made of lead glass. Even photochromic sunglasses have a considerable protective effect.

In any group of cardiologists the workload should be shared so that individuals avoid the risk of excessive doses. The Manchester group[4] suggested that about 1000 cardiac catheterisations, eight angioplasties, and 150 pacemaker implants was a sensible workload for five cardiologists who do not use special eye protection and who wish to avoid classification as designated radiation workers.

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*Br Heart J* 1986; 55: 423–7

# The aetiology and prognostic implications of reciprocal electrocardiographic changes in acute myocardial infarction

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SUMMARY The relations between reciprocal ST segment depression in the electrocardiogram and infarct size and 10 year prognosis were studied in 315 patients who survived for at least 28 days after a first anterior or inferior myocardial infarction. ST depression was more common in inferior infarcts (72%) than in anterior (37%) ones. It occurred more frequently in complicated infarcts and in the presence of considerable ST elevation. Patients experiencing second or third degree heart block were significantly more likely to show reciprocal changes. The rise in peak cardiac enzyme concentration was higher in patients showing ST depression. In patients with ST depression, peak creatine kinase concentration was 46% higher, aspartate aminotransferase was 39% higher, and lactate dehydrogenase 29% higher after correction for site and complications. A discriminant function analysis selected infarct site, peak aspartate aminotransferase, and magnitude of ST elevation as predictors of the occurrence of ST depression. Age, severity, and smoking status did not significantly improve discrimination. Despite larger increases in peak enzyme concentrations patients with ST depression had marginally fewer subsequent episodes of unstable angina or fatal or non-fatal infarction and a marginally lower 10 year death rate. Neither difference was statistically significant. ST depression occurring early in the acute phase of myocardial infarction is likely to be a reflection of electrophysiological changes taking place at the site of the infarct that is manifested in the contralateral surface of the heart. Other causes, however, such as transient ischaemia at the site of the reciprocal changes or extension of the infarct to contiguous areas cannot be excluded in all cases.

In acute myocardial infarction the characteristic elevation of the ST segment of the electrocardiogram is often accompanied by depression of the ST segment remote from the site of the infarction.

The aetiology of these reciprocal ST changes has been the subject of several conflicting reports. Three different explanations have been put forward to account for the phenomenon: (*a*) that reciprocal changes are an electrophysiological phenomenon in which the observed ST depression is the "rear view" of the classic ST elevation; (*b*) that ST depression is a product of myocardial necrosis or ischaemia remote from the site of infarction; (*c*) that ST depression is a result of the extension of the infarct beyond its stated site.

Most studies to date have been of small numbers of patients and have been confined to in hospital prognosis or short term outcome. In this study we report on the 10 year outcome of 315 patients. We address two questions: (*a*) Are reciprocal electrocardiogram changes associated with a greater enzymatically estimated infarct size? (*b*) Do patients with such changes show a long term morbidity or mortality different from patients without them?

## Patients and methods

The patients studied had all been entered into the St Vincent's Hospital Heart Study. This is a long term follow up study of consecutive 28 day survivors of a

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Accepted for publication 6 January 1986

first attack of unstable angina or myocardial infarction. From 1961 to 1975 the study recruited only men under 60 years. When recruitment of a second cohort began in 1978 women were included. For this study we selected patients admitted between March 1970 and December 1975 and between February 1978 and December 1980, inclusive, with a first anterior or inferior infarction. Patients admitted before 1970 were excluded because their hospital charts, which had been transferred to microfilm, frequently lacked complete electrocardiographic records. Patients admitted after 1980 were excluded because of the limited follow up available.

Myocardial infarction was defined as cardiac pain at rest with fresh Q waves in the electrocardiogram or a greater than twofold rise in cardiac enzymes (creatine kinase, lactic dehydrogenase, and aspartate aminotransferase) or both. Only patients with anterior or inferior infarctions were included. Anterolateral infarctions, infarctions at other sites, and infarctions at multiple sites were excluded because there were too few of them for analysis.

Age, sex, and smoking status were recorded. Regular smokers who had given up for three months or more were rated as ex-smokers. Electrocardiograms recorded during the patient's admission were examined. The magnitude of both ST elevation and depression was recorded for each lead of the electrocardiogram. A shift of 1·0 mm or more in two or more leads was taken as evidence of ST depression or elevation. The leads in which the largest depression and elevation occurred were noted, and the maximum size of both elevation and, where applicable, depression was recorded in mV.

Serial estimations of cardiac enzymes were examined and peak concentrations of creatine kinase, lactic dehydrogenase, and aspartate aminotransferase were recorded. Creatine kinase estimations were not available for patients recruited before 1978. Of the 20 complications included in our coronary care protocol, four occurred in 15 (4·8%) or more patients. These were: left ventricular failure, ventricular fibrillation, second or third degree heart block, and pericarditis. The analysis was confined to these complications.

Patients were seen at follow up clinic on three occasions in the first year after discharge and annually thereafter. The date of the first non-fatal reinfarction or episode of unstable angina was recorded. Unstable angina was defined as cardiac pain at rest and serial ST-T changes with no rise or a less than twofold rise in cardiac enzyme concentrations. Date and mode of death were recorded for fatal cases and dates on which survivors were last seen were noted.

## Results

The study group comprised 315 patients of whom 25 were women. A hundred and sixty men were admitted between March 1970 and December 1975 inclusive, and 155 patients (of both sexes) were admitted between February 1978 and December 1980 inclusive. The admissions were consecutive apart from 20 patients whose electrocardiographic records were incomplete. Twenty two patients with infarctions at sites other than anterior or inferior ones or at multiple sites were admitted during the study period but these patients were excluded from the analysis. There were 221 (70·2%) current cigarette smokers in the group; 29 (9·2%) had never smoked.

Table 1 shows the relation between ST depression and site of infarction. Reciprocal changes occurred in 71·9% of inferior infarcts and 37·2% of anterior infarctions ($p < 0{\cdot}0001$). Complications occurred in 44·6% of anterior and 53·9% of inferior infarctions. This difference is not statistically significant. ST depression occurred in 63·5% of complicated and 47·8% of uncomplicated infarctions ($p = 0{\cdot}007$).

Table 2 shows the relation between reciprocal changes and in hospital complications. Patients experiencing second or third degree heart block were significantly more likely to have ST depression. Fourteen of 15 patients experiencing second degree block had inferior infarcts and 13 of them

Table 1 *Relation of reciprocal ST depression to site and severity of infarction*

| | *Total* | *ST depression* | | |
|---|---|---|---|---|
| | | *Present* | *Absent* | *p** |
| All cases | 315 | 175 (55·6%) | 140 (44·4%) | |
| Site: | | | | |
| Anterior | 148 (47·0%) | 55 (37·2%) | 93 (62·8%) | <0·0001 |
| Inferior | 167 (53·0%) | 120 (71·9%) | 47 (28·1%) | |
| Severity: | | | | |
| Complicated | 156 (49·5%) | 99 (63·5%) | 57 (36·5%) | 0·007 |
| Uncomplicated | 159 (50·5%) | 76 (47·8%) | 83 (52·2%) | |

*Significance levels based on $\chi^2$ test

Table 2 *Relation of reciprocal ST depression to complications*

| | *Total* | *ST depression* | | |
|---|---|---|---|---|
| | | *Present* | *Absent* | *p* |
| All cases | 315 (100%) | 175 (100%) | 140 (100%) | |
| Left ventricular failure | 63 (20·0%) | 41 (23·4%) | 22 (15·7%) | NS |
| Ventricular fibrillation | 28 (8·9%) | 18 (10·3%) | 10 (7·1%) | NS |
| Second degree heart block | 15 (4·8%) | 14 (8·0%) | 1 (0·7%) | 0·006 |
| Third degree heart block | 14 (4·4%) | 12 (6·9%) | 2 (1·4%) | 0·041 |
| Pericarditis | 36 (11·4%) | 21 (12·0%) | 15 (10·7%) | NS |
| Ventricular extrasystoles | 33 (10·5%) | 16 (9·1%) | 17 (12·1%) | NS |

Table 3 *Relation of reciprocal changes to mean peak cardiac enzyme increase*

| | *CK (IU/l)* | *AST (IU/l)* | *LDH (IU/l)* |
|---|---|---|---|
| Number of cases | 130 | 291 | 292 |
| Mean:* | | | |
| ST depression | 1393 | 231 | 1244 |
| No ST depression | 956 | 166 | 966 |
| Significance of F | p=0·002 | p<0·001 | p<0·001 |

*Means are adjusted for site and severity.
Significance levels based on ANOVA with ST depression, site (anterior or inferior myocardial infarction), and severity as three orthogonal factors.
CK, creatine kinase; AST, aspartate aminotransferase; LDH, lactic dehydrogenase.

Table 4 *Factors discriminating between patients with reciprocal changes and patients without**

| *Factor* | *Percentage of variance explained* | *Standardised discriminant coefficient* |
|---|---|---|
| Presence of IMI | 11·9% | 0·8081 |
| Maximum AST rise | 7·6% | 0·4814 |
| Maximum ST elevation | 3·4% | 0·4596 |
| *Total % explained* | 22·9% | |

*Based on discriminant function analysis.
Factors not selected: age, severity, smoking status.
IMI, inferior myocardial infarction; AST, aspartate aminotransferase.

showed ST depression. Ten of 14 patients with third degree block had inferior infarcts and all but one showed ST depression.

Table 3 shows the relation between reciprocal changes and infarct size as estimated by peak enzyme rise. We used an analysis of variance with three orthogonal factors: presence of reciprocal changes, topography, and severity. Mean enzyme rise was significantly higher in patients showing reciprocal changes. When corrected for topography and presence of complications peak creatine kinase was 45·7% higher (p=0·002), aspartate aminotransferase was 39·2% higher (p<0·001), and lactate dehydrogenase 27·8% higher (p<0·001) in patients with ST depression than in those without. Complicated infarctions showed a significantly higher peak in all three enzyme concentrations independently of topography and presence of reciprocal changes. Site of infarction was not related to peak enzyme values independently of ST depression or severity.

We performed a discriminant function analysis to assess the relative value of size and site of infarction, age, presence of complications, and smoking status in predicting the occurrence of reciprocal changes. This is a statistical technique which selects the variables which discriminate best between two or more groups. We used a stepwise method in which variables are selected one at a time and selection is

Table 5 *Reciprocal ST depression and 10 year prognosis*

| | *ST depression* | | *p* |
|---|---|---|---|
| | *Present* | *Absent* | |
| Mortality (all causes): | | | |
| 5 year (SE) | 18·8% (3·2%) | 22·7% (3·7%) | |
| 10 year (SE) | 32·3% (4·7%) | 46·3% (5·6%) | |
| Ratio of observed to expected deaths: | 84·2% | 119·0% | 0·098 |
| CHD mortality: | | | |
| 5 year (SE) | 15·3% (3·0%) | 16·1% (3·2%) | |
| 10 year (SE) | 26·2% (4·3%) | 31·8% (6·7%) | |
| Ratio of observed to expected CHD deaths: | 93·6% | 107·9% | 0·558 |
| Fresh acute CHD rate: | | | |
| 5 year (SE) | 20·0% (3·3%) | 24·2% (4·1%) | |
| 10 year (SE) | 35·7% (4·9%) | 46·1% (7·0%) | |
| Ratio of observed to expected events: | 87·6% | 116·5% | 0·162 |

Significance levels based on logrank test. Rates and significances corrected for site and severity of infarction. CHD, coronary heart disease.

stopped when no other variable significantly increases the correlation between presence of reciprocal changes and the group of predictor variables. Three variables were selected (Table 4): site of infarction, which accounted for 11·9% of variance; peak aspartate aminotransferase, which added another 7·6% to the percentage of variance explained; and maximum size of ST depression, which added another 3·4%. Severity, age, and smoking status did not significantly increase the correlation further.

Table 5 shows the relation between reciprocal changes and 10 year outcome. When corrected for topography and severity there was a 35·7% rate of fresh acute coronary events in the group showing ST depression and a 46·1% rate in those without ($p = 0{\cdot}162$). Patients with reciprocal changes had a 32·3% 10 year death rate (Table 5), compared with 46·3% in patients without ($p = 0{\cdot}098$). There was no difference between the groups in 10 year mortality rate for coronary heart disease.

## Discussion

The current interest in reciprocal ST depression in patients with myocardial infarction has yielded several findings which are difficult to reconcile and which have led to widely differing conclusions. Some workers, using various invasive and non-invasive investigations, have concluded that reciprocal changes are not a measure of contiguous or remote ischaemia but reflect an electrical artefact associated with a current of injury at the infarct site.[1-7] Others believe that the reciprocal changes are associated with an extension of the infarct to contiguous areas,[8-12] whereas others conclude that the changes are evidence of ischaemia in the reciprocal area of the myocardium remote from the infarct site.[9 11 13-16]

There is some disagreement about the implications of reciprocal changes in relation to immediate and later morbidity and mortality. Nearly all workers who address the subject report a higher frequency of immediate complications in patients when such changes are present.[8-12]

Contrary to what might be expected in view of their greater infarct size, our patients with ST depression did not have a worse 10 year prognosis than those without ST depression. Among the few reports on long term outcome, Wasserman *et al*,[7] like ourselves, did not find an adverse effect while Hlatky *et al* did find a significantly higher long term mortality.[8] The higher mortality noted by Hlatky *et al* in patients with reciprocal ST changes might more reasonably have been expected.

The apparently contradictory findings of various researchers have so far failed to elucidate the nature and implications of reciprocal ST depression. The results which we have presented clarify some of these problems while raising issues for future research. In common with other studies we found that patients with greater ST elevation were more likely to exhibit reciprocal depression. We can also confirm the observation of Goldberg *et al* that patients with ST depression have significantly higher peak cardiac enzyme concentrations.[9] No other study, to our knowledge, has attempted to characterise the interrelation of several factors in predicting the occurrence of ST depression. In the patients we studied reciprocal changes were more common in inferior infarction and became more likely with both increasing infarct size and increasing magnitude of ST elevation.

It is important to distinguish between the transient reciprocal changes which occur early in the course of the infarction and resolve within 48 hours and persistent ST depression. This necessity is highlighted by the study of Gelman and Saltups who divided patients who displayed reciprocal changes into those whose ST depression resolved within 48 hours and those in whom the changes persisted.[17] The latter group showed a higher incidence of complications whereas the former showed a course similar to patients without reciprocal changes. Because we examined electrocardiogram records retrospectively we could not accurately assess the duration of reciprocal changes. As a result we have not been able to observe this distinction, and this limitation must be borne in mind.

The clear relation found between reciprocal changes and both infarct size and magnitude of ST elevation provides support for the view that reciprocal depression is an electrophysiological phenomenon reflecting changes at the infarct site, since it is most frequently observed in infarctions in which ST elevation is most pronounced. The frequency with which it occurs, particularly in inferior infarctions, argues against necrosis or ischaemia remote from the site of the main infarction, as does the absence of fresh Q waves in the reciprocal area. The reperfusional experiments of Little *et al* also support this hypothesis.[5] Other possible mechanisms include transient metabolic or hydraulic effects, or loss of compliance in the reciprocal area simulating an early subendocardial infarction.

The greater frequency of reciprocal changes in inferior infarction has not yet been adequately explained although it may simply be a reflection of the greater number of anterior leads available in the standard electrocardiogram.

Extension of the infarction to contiguous areas such as the posterolateral and inferolateral areas of the left ventricle or to the right ventricle in inferior infarction is a reflection of the size of infarct. Several studies support the view that such extension into contiguous areas is more frequent in the presence of reciprocal changes.[8, 13–15]

Because of the current diversity of findings and views on the subject further research is clearly necessary. Future studies should be prospective and should distinguish between transient and persistent ST depression. Both anterior and inferior infarcts should be included, using appropriate radionuclide and angiographic studies of myocardial infarction and perfusion. Finally, further long term follow up studies are needed to clarify the conflicting reports on the relation between reciprocal changes and subsequent morbidity and mortality.

The present study is a retrospective one specifically designed to examine long term morbidity and mortality. Because it is confined to 28 day survivors, it does not address issues concerning the relation of reciprocal changes to other factors and to outcome in the immediate post-infarction period. A substantial number of recent reports have studied this latter area, and they support our findings that reciprocal changes are positively related to size of infarct and to the frequency of complications during the acute phase. For this reason the immediate mortality of the patients with reciprocal changes in our study population may have been higher than that in those without ST depression. From the results presented, however, we can find no effect of reciprocal changes on prognosis, provided that the patient survives the initial 28 days after the infarction.

We thank Dr Ian Graham of the Meath and Adelaide Hospitals for his helpful suggestions, and the Computer Centre of University College Dublin for computing and word processing facilities.

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# U waves in ventricular hypertrophy: possible demonstration of mechano-electrical feedback

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SUMMARY The relation between ventricular function and electrocardiographic evidence of hypertrophy (by voltage criteria, "strain", and U wave inversion) was examined by means of M mode echocardiography and apex cardiography in 73 patients with diseases associated with left ventricular hypertrophy and 10 normal volunteers. In patients with disease, left ventricular cavity dimension and fractional shortening were unrelated to electrocardiographic findings, but left ventricular posterior wall thickness was greater in those with strain or U wave inversion. Without U wave inversion, hypertrophy and strain were weakly related to diastolic abnormalities, but the addition of U wave inversion was strongly associated with a reduced rate of early diastolic posterior wall thinning, prolonged isovolumic relaxation time, delayed mitral valve opening after minimum cavity dimension, and a pronounced increase in transverse dimension during the isovolumic period suggesting incoordinate relaxation.

It is concluded that, whereas a negative U wave frequently occurs in association with the pattern of left ventricular hypertrophy or strain, it alone is strongly related to abnormalities of isovolumic relaxation. The close relation between incoordinate relaxation and U wave inversion, events which occur virtually simultaneously during the isovolumic period, suggests a mechanical influence on U wave genesis.

U wave abnormalities rarely occur alone.[1] More prominent and better understood changes in the QRS complex and ST–T segment frequently overshadow associated U wave alterations, which as a result are often neglected. This would not be of consequence unless an added U wave abnormality provided further diagnostic information. U wave inversion, the best recognised U wave abnormality, is believed almost always to signify heart disease; its commonest associations are hypertension, coronary artery disease, and aortic or mitral valve disease, all of which have well recognised and clinically important effects on ventricular diastole.[2] Excluding coronary artery disease, left ventricular hypertrophy characterises this group of patients in some of whom we have previously described the significance of a superimposed "strain" pattern.[3] Another reason for examining the U wave in more detail is that it is the only part of the ventricular electrocardiographic complex that is recorded predominantly or exclusively in diastole, and thus may be expected to relate more closely to mechanical events in diastole.[4] The present study of such patients was aimed at investigating the relation between diastolic events on the one hand and the electrocardiographic changes of hypertrophy, strain, and U wave inversion on the other. Further, it was hoped that any correlation might contribute towards refining current perceptions about the genesis of the U wave which remain unclear.

## Patients and methods

### STUDY GROUPS

Eighty three subjects were divided into four groups according to electrocardiographic diagnoses (Table 1). These were 10 normal volunteers with normal electrocardiograms and 73 patients with heart disease of whom 15 had left ventricular hypertrophy on voltage criteria alone, 20 had left ventricular hypertrophy with strain, and 38 had U wave

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Accepted for publication 6 January 1986

Table 1 *Electrocardiographic diagnoses*

| *Group* | *Number of patients* |
|---|---|
| Normal (N) | 10 |
| Left ventricular hypertrophy (H) | 15 |
| Left ventricular hypertrophy + strain (S) | 20 |
| Left ventricular hypertrophy + strain + U wave inversion (U) | 38 |

inversion with left ventricular hypertrophy or strain. All had sinus rhythm with normal intraventricular conduction.

As U wave interpretation is difficult and unreliable at heart rates below 50 beats/min or above 100 beats/min,[5 6] patients with such rates were excluded from the study. When the heart rate is 50–100 beats/min normal U waves may be identified in several leads as a positive deflection smaller than and following the T wave. The U wave is normally negative in aVR. The interval between the apices or nadirs of a T and U wave complex is, as a rule, 150 ms or more, and this relation is used to distinguish U waves from bifid T waves.[7] Further, the onset of the U wave usually coincides with the second heart sound which also marks the completion of the T wave.

### CRITERIA

The following criteria were adopted (see Fig. 1): (1) left ventricular hypertrophy was diagnosed when at least one of the following criteria, modified after Romhilt and Estes,[8] was met (*a*) SV1 + RV5/6 > 35, (*b*) RV5/6 > 26, (*c*) R1 + S3 > 25, (*d*) RaVL > 11, (*e*) SaVR > 14 (units are mm); (2) a strain pattern was identified as ST segment depression (> 1·0 mm) and T wave flattening or inversion in the lateral or inferior leads[3]; (3) U wave inversion was considered to be present if a discrete negative deflection was consistently seen within the T–P segment in leads in which the U wave is normally positive. Negativity was judged with reference to the ensuing PR segment.[1 9] Since the normal U wave is negative in lead aVR, an upright U wave there denotes U wave inversion.

### CLINICAL DIAGNOSES

Table 2 shows the study population categorised by clinical diagnoses. Patients with hypertrophic cardiomyopathy were included on the grounds that in such cases left ventricular hypertrophy is always present, subaortic stenosis often occurs, and U wave inversion is a known association.[2]

### ELECTROCARDIOGRAPHY

Within seven days of echocardiography standard 12 lead electrocardiograms were recorded by means of a Hewlett-Packard (model 1511B) single channel or a Cambridge (model 3058/2) Series C three channel recorder with patients in the supine position and during quiet respiration. In addition to measurements made to see whether the criteria for left ventricular hypertrophy were met, the following were determined: (*a*) QQ (or RR) interval and heart rate (*b*) QT interval taken from the initial QRS deflection to the end of the T wave (from this, the QTc was derived using the formula, $QTc = QT\sqrt{RR}$); and (*c*) QaU interval measured from the initial QRS deflection to the apex or nadir of the U wave. No measurements were made on extrasystoles and postextrasystoles. For each interval the average of two measurements was calculated. The electrocardiogram was interpreted and measured before digitised information from echocardiography was analysed. Heart rates from the electrocardiogram were compared with those from the echocardiogram.

### ECHOCARDIOGRAPHY

M mode echocardiograms were recorded with Cambridge Instruments equipment or an Advanced Technology Laboratories (ATL) Mark 300 machine with a 2·25 or 3·0 MHz transducer. The patients were studied in the left semilateral position, and simultaneous electrocardiograms and phono-

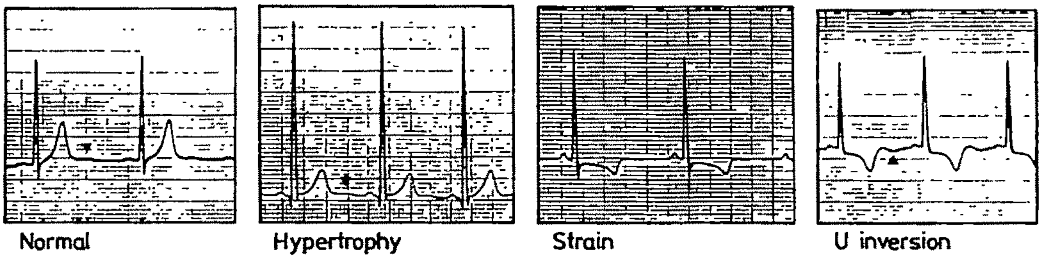

Fig. 1 *Single leads (lateral precordial) from electrocardiograms showing normality, hypertrophy on voltage criteria, strain pattern, and strain pattern with U wave inversion. Arrowheads point to the first U wave in each example; no U waves are present in the example of strain alone. Rapid QRS deflections that do not register sufficiently boldly for reproduction purposes have been darkened.*

cardiograms were recorded at a paper speed of 100 mm/s. Simultaneous apex cardiograms were also recorded in 27 of the patients with heart disease. Records of the left ventricular cavity were taken at the level of the tips of the mitral leaflets showing cusp separation. Here both cusps were visible at the onset of diastolic separation and early diastole, but not during the remainder of diastolic filling. Aortic valve closure ($A_2$) was taken as the onset of the first high frequency vibration of the second heart sound. $A_2$ was not recognised in many patients with aortic stenosis. The O point of the apex cardiogram was identified in the usual way as a sharp early diastolic nadir. Echocardiograms were digitised by means of a Summagraphics digitiser and a Prime 750 computer system. Two or, if available, three optimally recorded cardiac cycles were digitised so that mean values could be calculated. The following measurements were obtained: (1) maximum (Dd) and minimum (Ds) left ventricular dimension, and fractional shortening (%) calculated as 100(Dd−Ds)/Dd; (2) thickness of left ventricular posterior wall (PWd) at the onset of the QRS; (3) peak value of normalised rate of dimension (D) increase, calculated as 1/D.dD/dt (NPRDI), during early diastole; (4) normalised peak rate of posterior wall thinning (NPRWT) during early diastole calculated in the same way; (5) the following time intervals (*a*) cycle length, from which the echocardiographic heart rate was derived, (*b*) $A_2$ to mitral valve opening ($A_2$–MVO) which is the period of isovolumic relaxation, (*c*) left ventricular minimum dimension to mitral valve opening (MD–MVO), (*d*) O point to the time of peak rate of left ventricular dimension increase (O–PRDI), (*e*) interval from the onset of the QRS to the time of minimum dimension (QMD), (*f*) interval from the onset of the QRS to mitral valve opening (QMVO), (*g*) interval from the onset of the QRS to the O point (QO), (*h*) interval from onset of the QRS to the time of peak rate of dimension increase (QPRDI); and (6) the percentage of dimension increase occurring during the interval from minimum dimension to mitral valve opening (%DI,MD–MVO).

Table 2 *Clinical diagnoses*

| *Diagnoses* | *Number of patients* |
|---|---|
| Hypertrophic cardiomyopathy | 20 |
| Aortic valve stenosis | 21 |
| Aortic valve stenosis, coarctation of aorta | 2 |
| Supravalvar aortic stenosis | 3 |
| Coarctation of aorta | 4 |
| Systemic hypertension | 10 |
| Aortic valve stenosis and regurgitation | 3 |
| Aortic regurgitation | 5 |
| Mitral regurgitation | 3 |
| Idiopathic left ventricular hypertrophy | 2 |
| Normal volunteers | 10 |
| Total | 83 |

Table 3 *Electrocardiographic findings and time intervals (ms)*

| | *U* | *S* | *H* | *N* |
|---|---|---|---|---|
| Number of subjects | 38 | 20 | 15 | 10 |
| Voltage, SV1 + RV5/6 (mm) | 42 (14) | 38 (13) | 41 (49) | 26 (6) |
| QQ | 844 (52) | 868 (95) | 911 (120) | 920 (152) |
| QT | 429 (47) | 425 (38) | 423 (33) | 427 (31) |
| QTc | 395 (72) | 396 (50) | 404 (52) | 425 (59) |
| $QA_2$ | 435 (77) | 442 (54) | 424 (34) | 440 (21) |
| QMD | 432 (76) | 442 (62) | 423 (54) | 463 (31) |
| QMVO | 534 (78) | 516 (61) | 486 (58) | 502 (24) |
| QaU | 524 (52) | 528 (49) | 518 (50) | 522 (34) |
| QO* | 533 (57) | 541 (26) | 521 (34) | NA |
| QPRDI | 479 (55) | 530 (45) | 531 (22) | NA |

*Data from 27 subjects with apex cardiograms.
Groups U, S, H, and N as in Table 1
NA, not available. Mean values are given with standard deviation in parentheses. $QA_2$, interval from onset of QRS to aortic second sound; QMD, interval from onset of QRS to time of minimum dimension; QMVO, interval from onset of QRS to mitral valve opening; QaU, interval from initial QRS deflection to apex or nadir of U wave, QO, interval from onset of QRS to O point; QPRDI, interval from onset of QRS to time of peak rate of dimension increase.

### STATISTICAL METHODS

Five electrocardiographic, five combined electrocardiographic and echocardiographic, and nine echocardiographic variables (Tables 3 and 4) were selected for statistical analysis. Data are expressed as mean (1 SD). For each variable, detection of significant differences among the four defined study groups was performed by a one way analysis of variance (ANOVA). Where appropriate, mean values of individual pairs were compared by Student's *t* (unpaired) test. A p value of $< 0.05$ was regarded as significant.

## Results

To avoid lengthy repetition, the study groups are identified by the initials U (U wave inversion), S (strain), H (hypertrophy), and N (normals) as described in Table 1.

### ELECTROCARDIOGRAPHY

Of 73 subjects with heart disease, 38 (group U) had U wave inversion, with strain present in all but three patients (Table 3). In the 35 subjects without an inverted U wave, the strain pattern was present in 20 (group S), while 15 (group H) had only hypertrophy on voltage criteria. All 10 normal volunteers (group N) had no electrocardiographic abnormality. Voltage (SV1 + RV5/6, in mm) was not significantly different among groups U, S, and H, but was greater than normal in group U ($p < 0.001$), group S ($p < 0.01$), and group H ($p < 0.001$). The QQ interval in

Table 4 *Echocardiographic findings*

| *Finding* | *U* | *S* | *H* | *N* |
|---|---|---|---|---|
| LV diastolic dimension (mm) | 45 (12) | 48 (8) | 50 (12) | 48 (3) |
| LV posterior wall thickness (mm) | 14 (4) | 14 (3) | 12 (4) | 10 (1) |
| LV fractional shortening (%) | 31 (10) | 30 (8) | 35 (8) | 36 (4) |
| NPRDI (cm/s) | 2·3 (1·0) | 2·4 (0·8) | 2·9 (1·1) | 3·1 (0·8) |
| NPRWT (cm/s) | 2·8 (1·1) | 3·6 (1·5) | 3·9 (1·7) | 5·4 (1·7) |
| $A_2$–MVO (ms)* | 95 (33) | 76 (26) | 69 (31) | 62 (14) |
| MD–MVO (ms) | 101 (31) | 74 (31) | 63 (41) | 39 (22) |
| %DI,MD–MVO | 28 (13) | 19 (12) | 14 (7) | 7 (5) |
| O–PRDI (ms)† | −54 (41) | −11 (48) | 10 (40) | NA |

*Does not include data from 14 subjects without a detectable $A_2$.
†Data from 27 subjects with apex cardiograms.
NA, not available. Mean values are given with standard deviation in parentheses. LV, left ventricular; NPRDI, normalised peak rate of dimension increase; NPRWT, normalised peak rate of posterior wall thinning; $A_2$–MVO, $A_2$ to mitral valve opening; MD–MVO, left ventricular minimum dimension to mitral valve opening; O–PRDI, O point to time of peak rate of left ventricular dimension increase.

groups U and S was shorter than normal ($p < 0·05$). No differences between the groups were present for the QT, QTc and QaU intervals. The mean (SD) heart rates measured from the electrocardiogram (70 (12) beats/min) and echocardiogram (68 (13) beats/min) were similar.

### ELECTROCARDIOGRAPHY AND ECHOCARDIOGRAPHY

There were no significant differences among the four groups (Table 3) for any of the time intervals measured from the onset of the QRS to the aortic second sound ($QA_2$), to minimum dimension (QMD), to mitral opening (QMVO), and to the O point (QO). The interval from the QRS to the peak rate of dimension increase (QPRDI) was shorter in group U compared with that in group H ($p < 0·05$), but not with that in group S ($p = 0·051$). The mean values for $QA_2$ and QMD were virtually identical in groups U, S, and H, but $QA_2$ was approximately 20 ms earlier than QMD in the normals.

### ECHOCARDIOGRAPHY

Table 4 summarises the results for the nine echocardiographic measurements. There were no significant differences between groups in left ventricular cavity dimension and fractional shortening. Posterior wall thickness was greater than normal ($p < 0·01$) in group U and group S but not in group H ($p = 0·074$).

Unlike the three basic echocardiographic indices just described, the last six (Table 4) reflect events in early diastole—the period during which the U wave is registered. It was only in these diastolic measurements that differences were observed between groups U and S. Group U is distinguished from group S solely by the presence of U wave inversion in the former. Compared with left ventricular hypertrophy with strain (group S), the presence of U wave inversion (group U) was associated with a reduced normalised peak rate of left ventricular posterior wall thinning ($p < 0·05$), a longer isovolumic relaxation period ($p < 0·05$), a longer interval from minimum left ventricular dimension to mitral valve opening ($p < 0·01$), and greater dimension increase during MD–MVO ($p < 0·05$). Directionally similar but larger differences were present for each of these measurements when group U was compared with group H (NPRWT, $p < 0·05$; $A_2$–MVO, $p < 0·05$; MD–MVO, $p < 0·001$; %DI,MD–MVO, $p < 0·001$) or group N (NPRWT, $p < 0·001$; $A_2$–MVO, $p < 0·01$; MD–MVO, $p < 0·001$; %DI,MD–MVO, $p < 0·001$). None of these variables was significantly different in the group with hypertrophy alone (group H) and the group with an added strain pattern (group S). Compared with normal individuals, however, both these groups had reduced peak rate of wall thinning ($p < 0·01$ for group S, $p < 0·05$ for group H) and greater percentage of dimension increase during MD–MVO ($p < 0·01$ for group S, $p < 0·05$ for group H), while MD–MVO itself was significantly prolonged only for group S ($p < 0·01$). The normalised peak rate of left ventricular dimension increase was not different among groups U, S, and H, but was decreased in group U ($p < 0·05$) and group S ($p < 0·05$) compared with normal. Peak rate of left ventricular dimension increase with respect to the O point occurred earlier, becoming more negative, in group U compared with group H ($p < 0·01$) but not with

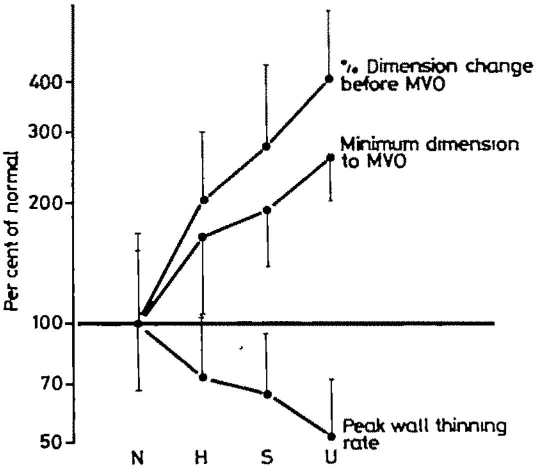

Fig. 2 *Graph comparing the mean values of three diastolic variables in groups with hypertrophy (H), strain (S), or U wave inversion (U) with normal (N). Vertical extensions represent one standard deviation. MVO, mitral valve opening.*

group S ($p = 0.061$) although the difference was almost significant.

In addition to individual comparisons, Table 4 shows that mean values for each of the six diastolic measurements progress in a stepwise manner from N to H to S to U. Fig. 2 illustrates this consistent trend for three of the measurements.

Subset analysis was performed on the largest diagnostically homogeneous group—21 patients with isolated aortic valve stenosis. Of these, 12 had U wave inversion, six had strain, and three had hypertrophy on voltage criteria. Compared with strain alone, U wave inversion was associated with reduced peak rate of wall thinning (2·2 cm/s *vs* 3·2 cm/s, $p < 0.05$) and greater dimension increase during the interval from left ventricular minimum dimension to mitral valve opening (MD–MVO) (32% *vs* 18%, $p < 0.05$); the difference for the MD–MVO interval (103 ms *vs* 78 ms, $p = 0.060$) approached statistical significance. The interval from $A_2$ to mitral valve opening was not compared because a discrete $A_2$ could not be identified in many of these patients. Too few apex cardiograms were available to allow meaningful comparisons of the interval from the O point to time of peak rate of left ventricular dimension increase. The subgroup of three patients with hypertrophy alone was too small for analysis.

## Discussion

Almost thirty years ago in his clinical study of hypertensive patients Kemp *et al* pointed out that U wave inversion commonly accompanied the pattern of left ventricular strain in the electrocardiogram.[10] Compared with strain alone, additional U wave inversion was associated with a higher incidence of cardiomegaly, cardiac failure, uraemia, cerebrovascular accidents, encephalopathy, and deaths. In worsening disease, serial electrocardiograms may show stepwise evolution of hypertrophy, strain, U wave flattening and, finally, inversion.[6 10] It was proposed then that "an inverted U wave was a late finding in left ventricular strain patterns . . . associated with clinical findings of more advanced disease of the left ventricle."

The left ventricular strain pattern does not result from an increase in left ventricular mass since athletes with substantial cardiac hypertrophy do not manifest it. Further, while the strain pattern is only weakly, if at all, related to abnormalities of systolic function, it is closely correlated with diastolic abnormalities.[3] Since ST and T deflections are generally completed before mechanical diastole begins, this correlation must be an indirect one, perhaps due to a direct factor nested within the strain group.

The present study suggests that this additional factor is closely related to U wave inversion. In the absence of a negative U wave, the strain pattern is only weakly related to diastolic abnormalities. By contrast, addition of U wave inversion was associated with reduced diastolic wall thinning rate, a prolonged isovolumic relaxation period, and delayed mitral valve opening relative to minimum dimension. During this period between minimum dimension and the start of left ventricular filling, significant dimension increase occurred when U wave inversion was present, amounting to almost a third of total dimension increase for diastole. Such an increase in transverse dimension during a period of constant volume indicates correspondingly large reductions in other axes, implying the presence of incoordinate relaxation. Since the U wave, whether upright or inverted, begins at about $A_2$ or minimum dimension, and reaches a peak or a trough at approximately mitral valve opening, its proximal limb has a consistently close temporal relation with the isovolumic relaxation period. Thus, not only is U wave inversion associated with incoordinate wall movement, but both are virtually simultaneous events during isovolumic relaxation, compatible with a direct relation between the two. If causal, it is likely that mechanical events are primary since the U wave has no known excitation-contraction function. Contraction-excitation feedback, though less conspicuous than excitation-contraction coupling, has been shown to occur.[11] Lab suggested that mechanical inhomogeneities in the intact ventricle after repolarisation is complete generate current flow or afterpotentials following the T wave, and thus form or influence the U wave. Differences in electrical potential between muscle regions with varying degrees of contraction-excitation feedback due to inhomogeneous wall movement may determine the U wave vector.[12] Our finding that incoordinate relaxation is associated with reversal of U wave polarity thus provides strong support for this hypothesis.

To date, the mechanism of even the normal U wave remains controversial.[2] Lepeschkin, in an early review,[13] discussed three possibilities: first, that it results from a longer duration of the action potential in some part of the ventricles, variously thought to be Purkinje fibres,[14] papillary muscles,[15] or the basal wall of the ventricles[16]; second, that it reflects afterpotentials following the action potential; and third, that it is caused by potentials generated by stretching of the ventricular muscle during the phase of rapid filling during early diastole. He argued that the morphology of the U wave was not consistent with the first explanation, and pointed out that amphibians showed U waves despite lacking Purkinje fibres. Subsequent observations suggest that the second and third theories may in fact be components of a single explanation that attributes the U wave to a "stretch-afterpotential".[7] This concept is provided with a firmer basis by Lab's experimental demonstration of contraction-excitation potentials in the intact ventricle, and is extended by our observations of the link between disordered diastolic mechanics and U wave behaviour.

The exact nature of the entity "stretch" has not been clearly defined. Presumably it must depend on the extent of lengthening, but may also be related to the tension in the muscle affected. It may thus be relevant that the peak rate of dimension increase tends to occur before the O point when the U wave is inverted, and progressively later with lesser electrocardiographic abnormalities. Since ventricular pressures are higher before rather than after the O point, which approximates to the nadir of ventricular diastolic pressure,[17] increase of dimension occurs at higher pressures in those with negative U waves. This may be a further factor leading to the development of abnormal surface potentials after repolarisation in patients with left ventricular hypertrophy and U wave inversion.

The extent of the various diastolic abnormalities in our study population appears to follow consistently the electrocardiographic progression from normal to hypertrophy to strain and to U wave inversion. This parallels the clinical observations of Kemp *et al*[10] and reinforces the concept that U wave inversion represents a more advanced stage of left ventricular disease. More important, a negative U wave may be an electrocardiographic sign of diastolic dysfunction.

In patients with left ventricular hypertrophy, U wave inversion is fairly stable although regression is possible.[18] Stable U wave inversion may also be seen in resting electrocardiograms of patients with coronary artery disease, particularly of the left anterior descending coronary artery.[9] Incoordinate relaxation is also a feature of coronary artery disease.[19]By contrast, transient U wave inversion may appear during infusion of pressors, exercise, and attacks of variant angina.[7 20 21] Therefore it appears that the common factor influencing U wave behaviour may be chronically present or acutely induced. Clearly it is not primarily dependent on changes such as fibrosis or ischaemia. Rather, the underlying mechanism is more likely to be a dynamic one which, for the moment, appears to be best explained by the hypothesis that the U wave is closely related to, if not actually an expression of, the pattern of regional ventricular wall kinetics during isovolumic relaxation. If so, greater attention to techniques of U wave recording and interpretation may provide easily obtained and clinically useful clues to important alterations in diastolic function.

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# Altered platelet $\alpha_2$ adrenoreceptor in acute myocardial infarction and its relation to plasma catecholamine concentrations

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SUMMARY Changes in platelet $\alpha_2$ adrenoreceptors and their relation to plasma catecholamine concentrations were studied in 11 patients with acute transmural myocardial infarction. A radiolabelled $\alpha_2$ adrenoreceptor antagonist, [$^3$H]-yohimbine, was used to assay $\alpha_2$ adrenoreceptors on platelet membranes, and plasma catecholamine concentrations were measured by high performance liquid chromatography. The number of platelet $\alpha_2$ adrenoreceptors, the dissociation constant, and plasma noradrenaline and adrenaline concentrations were studied 6·6 (3·3) (mean (SD)) hours after the onset of acute myocardial infarction and one month later. The mean (SD) number of adrenoreceptors increased significantly from 94·5 (50·5) fmol/mg protein immediately after infarction to 157·0 (65·7) fmol/mg protein one month later. The dissociation constant, however, did not change significantly (4·33 (1·40) nmol/l *vs* 4·37 (1·22) nmol/l). Raised noradrenaline (5·60 (4·37) nmol/l) and adrenaline (0·28 (0·14) nmol/l) concentrations had fallen significantly to normal values (1·21 (0·67) and 0·09 (0·05) nmol/l respectively) a month after infarction. The decrease in the number of $\alpha_2$ adrenoreceptors soon after infarction may be beneficial because such a change will reduce the strength of various reactions to catecholamines, such as vasoconstriction.

Human platelets have been used to investigate the possible role of $\alpha_2$ adrenoreceptors in disease because they are easily obtained and their membranes contain $\alpha_2$ adrenoreceptors.[1] In patients with angina pectoris the number of platelet $\alpha_2$ adrenoreceptors was reported to be significantly lower when patients had symptoms than when they did not.[2] The number of $\alpha_2$ adrenoreceptors did not correlate with plasma noradrenaline concentrations. Changes in the number of $\alpha_2$ adrenoreceptors in acute myocardial infarction have not been studied. This is likely to be an important factor because $\alpha_2$ adrenoreceptors may affect coronary artery tone.

We used a radioligand binding technique to study $\alpha_2$ adrenoreceptors in patients with acute myocardial infarction and we investigated the possibility of a relation between changes in receptor number or affinity and plasma catecholamine concentrations.

## Patients and methods

### PATIENTS

We studied 11 patients (seven men) with a first acute transmural myocardial infarction. The infarction was anterior in five patients and inferior in six. They were selected from a consecutive series of 18 patients with acute myocardial infarction admitted to this hospital between May and September 1984. Two patients with cardiogenic shock and three with heart failure were excluded, as were two patients who underwent coronary artery bypass operation. The diagnosis of acute transmural myocardial infarction was based on the acute onset of chest pain that lasted for more than 30 minutes and was unresponsive to

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Accepted for publication 29 January 1986

glyceryl trinitrate, and on ST segment elevation >2mV in the standard 12 lead electrocardiogram. The diagnosis was subsequently confirmed by the evolution of typical electrocardiographic changes and an increase in creatine kinase MB isoenzyme.

One patient (case 4) had had angina before infarction and had been treated mainly with sublingual glyceryl trinitrate. One patient (case 9) had been taking a thiazide for hypertension. No patient had been given $\beta$ receptor blocking agents. After admission all patients were given nitrates. Five patients (cases 3, 5, 7, 10, and 11) were treated with diltiazem. Catecholamines and $\beta$ receptor blocking agents were not given to any patients. No patient had chest pain or showed signs of heart failure while in hospital. None had enzymatic or electrocardiographic evidence of a recurrence of acute myocardial infarction.

### BLOOD SAMPLING AND ISOLATION OF PLATELET MEMBRANES

Blood was drawn from an antecubital vein immediately after admission (6·6 (3·3) hours after the onset of chest pain). Three patients (cases 1, 5, and 9) were initially in Forrester haemodynamic subset II and eight were in subset I. Patients in group I were given frusemide which improved their haemodynamic condition. Blood samples were taken a month after the onset of infarction. All medication was discontinued for at least 24 hours before the second blood samples were collected.

Platelet membranes were obtained by the method of Garcia-Sevilla *et al.*[3] Blood (30–40 ml) was collected in acid citrate dextrose (8:1, vol/vol). The sample was centrifuged at 160*g* for 10 minutes at 25°C, and the platelet rich plasma was titrated to pH 6·5 with the acid citrate dextrose solution. Plasma was then recentrifuged at 5100*g* for 15 minutes at 25°C to obtain a platelet pellet. The pellet was washed twice by 5 ml of Tyrode's buffer (sodium chloride 137 mmol/l, potassium chloride 2·7 mmol/l, monobasic sodium phosphate 0·36 mmol/l, magnesium chloride 0·01 mmol/l, sodium bicarbonate 12·0 mmol/l, dextrose 0·56 mmol/l, pH 8·0) and recentrifuged for 15 min at 5100*g*. The pellet was lysed by homogenisation in 3 ml of ice cold hypotonic buffer (TRIS edetic acid 5 mmol/l, pH 7·5). The platelet membranes were obtained by centrifugation at 39 000*g* for 10 min and then resuspended in the TRIS incubation buffer (TRIS-hydrochloric acid 50 mmol/l, magnesium chloride 10 mmol/l, pH 7·5) used in the radioligand binding assay.

### RADIOLIGAND BINDING ASSAY

We used [$^3$H]-yohimbine (New England Nuclear, Boston, Massachusetts), an $\alpha_2$ adrenoreceptor antagonist to measure total radioligand binding in 0·1 ml volumes of fresh platelet membranes (0·15 (0·1) mg protein). Samples were incubated in duplicate at 25°C for 20 minutes. Non-specific binding was measured by adding unlabelled yohimbine (10 $\mu$mol/l) to other duplicate samples. Specific binding was calculated as the difference between total and non-specific binding. Incubations were terminated by adding 5 ml of the TRIS-incubation buffer to the samples. The membrane bound tritiated ligand was recovered by rapid filtration of the diluted sample under vacuum through Whatman GF/C glassfibre filters. The filters were washed twice with 10 ml of TRIS-incubation buffer, air dried, and counted for radioactivity as described by Smith *et al.*[4] Protein concentrations were determined by the method of Lowry *et al.*[5] We used Scatchard analysis of the saturation isotherms to determine the maximal number of binding sites (*x* intercept of a plot of specifically bound ligand *vs* bound/free ligand) and the dissociation constant (negative reciprocal of the slope of the regression line).[6]

### PLASMA NORADRENALINE AND ADRENALINE

Plasma concentrations of noradrenaline and adrenaline were determined by the method of Yui *et al.*[7]

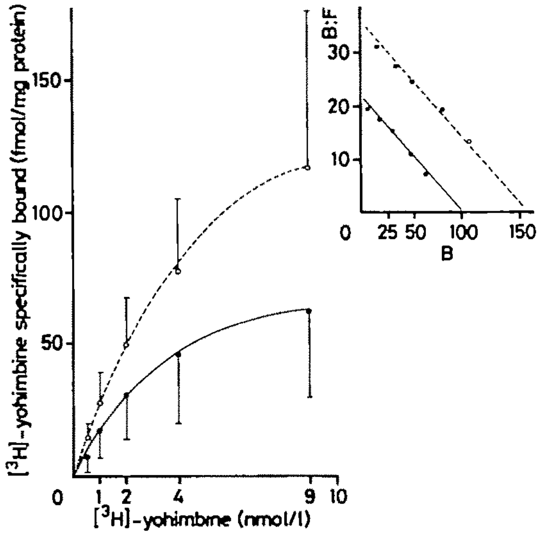

Fig. 1 *Specific binding of* [$^3$*H*]*-yohombine to platelet membranes from patients with acute myocardial infarction, soon after the onset (solid line) and one month later (dashed line) as a function of increasing concentrations (0·5 to 9 nmol/l) of the ligand. Inset: Scatchard plot showing the change in numbers of binding sites. B, specifically bound ligand; B:F, specifically bound ligand:free ligand.*

Table *Patient profile and summary of data*

| *Case* | *Age/sex* | *Medication* | **Angina* | *Kd (nmol/l)* | | *Bmax (fmol/mg protein)* | | *Noradrenaline/adrenaline (nmol/l)* | | *Clinical course* | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | *Soon†* | *1 month* | *Soon* | *1 month* | *Soon* | *1 month* | *Forrester subset* | *Treatment after admission* |
| Anterior myocardial infarction | | | | | | | | | | | |
| 1 | 62/M | None | (−) | 3·57 | 4·01 | 36·4 | 118·8 | 6·27/0 33 | 1·95/0·05 | II→I | GTNO, LISDN, frusemide |
| 2 | 54/F | None | (−) | 4·00 | 4 46 | 118·0 | 211·0 | — | — | I | LISDN |
| 3 | 38/M | None | (−) | 6·58 | 6 10 | 135·1 | 136·5 | 1·83/0·11 | 0 89/0·11 | I | LISDN, diltiazem |
| 4 | 77/M | Sublingual GTN | (+)‡ | 6 71 | 6 71 | 112 9 | 250·0 | 4·56/0 33 | 2 31/0 05 | I | LISDN |
| 5 | 74/F | None | (−) | 3 11 | 3·45 | 58 0 | 80·4 | 5·68/0·33 | 0·53/0·16 | II→I | LISDN, diltiazem, frusemide |
| Inferior myocardial infarction: | | | | | | | | | | | |
| 6 | 49/M | None | (−) | 5·18 | 4·98 | 88 3 | 137·2 | 5·44/0·16 | 0 71/0 05 | I | LISDN |
| 7 | 73/F | None | (−) | 3 60 | 3 86 | 93 3 | 267 0 | 16 34/0 49 | 1·83/0 05 | I | LISDN, diltiazem |
| 8 | 69/F | None | (−) | 5 38 | 4 27 | 55 2 | 115·6 | — | — | I | LISDN |
| 9 | 78/M | Thiazide | (−) | 3·53 | 4 48 | 61·4 | 62 4 | 5·68/0 44 | 1·42/0·05 | II→I | LISDN, frusemide |
| 10 | 57/M | None | (−) | 3 17 | 2 66 | 219·2 | 181 2 | 2·49/0·11 | 0 59/0·16 | I | LISDN, diltiazem |
| 11 | 56/M | None | (−) | 2 80 | 3·05 | 83 6 | 167·9 | 2·07/0·22 | 0 71/0 05 | I | LISDN, diltiazem |
| Mean | 62 5 | | | 4 33 | 4 37 | 96·5 | 157·0 | 5 60/0 28 | 1·21/0 09 | | |
| SD | 13 | | | 1·40 | 1·22 | 50·5 | 65·7 | 4·37/0·14 | 0·67/0 05 | | |

Bmax, maximal number of binding sites; Kd, dissociation constant; I and II, Forrester haemodynamic subset I and II; GTNO, glyceryl trinitrate ointment; LISDN, long acting isosorbide dinitrate.

*Before admission.

†Before onset of myocardial infarction

‡Angina lasting for two weeks before onset of myocardial infarction.

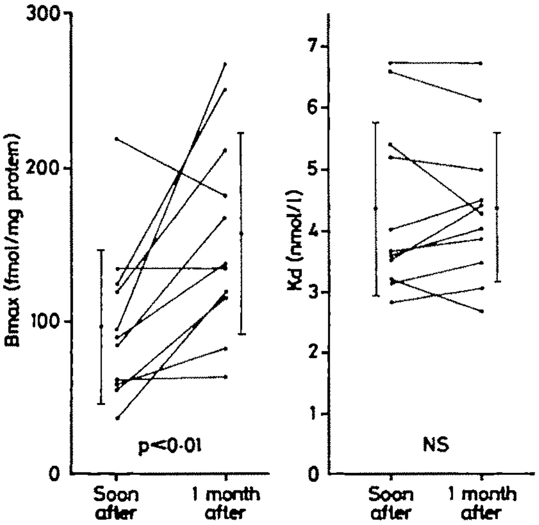

Fig. 2 *Alpha$_2$ adrenoreceptor number (Bmax; fmol/mg protein) and dissociation constant (Kd; nmol/l) in patients with acute myocardial infarction soon after and one month after onset.*

Normal values are 1·24–0·89 nmol/l and 0·16–0·05 nmol/l respectively.

### STATISTICAL ANALYSIS

Values are given as means and standard deviations. Statistical analysis was performed by Student's *t* test. Significance was defined as $p<0·05$.

## Results

### BINDING DATA

Figure 1 shows that the specific binding of [$^3$H]-yohombine to platelet membranes from patients was both saturable and of high affinity. The Table shows data for individual patients. The number of the adrenoreceptors increased significantly from 96·5 (50·5) fmol/mg protein early (6·6 (3·3) hours) after infarction to 157·0 (65·7) fmol/mg protein one month later ($p<0·01$) (Fig. 2). But there was no significant difference in the dissociation constant (4·33 (1·40) nmol/l *vs* 4·37 (1·22) nmol/l).

### PLASMA CONCENTRATIONS OF NORADRENALINE AND ADRENALINE

Plasma concentrations of noradrenaline and adrenaline were measured in nine of 11 patients. They were raised immediately after infarction, but they had fallen significantly one month later (noradrenaline from 5·60 (4·37) nmol/l to 1·21 (0·67) nmol/l, $p<0·05$; adrenaline from 0·28 (0·14) nmol/l to 0·09 (0·05) nmol/l, $p<0·05$). Changes in receptor number and concentrations of noradrenaline and epinephrine were not significantly correlated (noradrenaline $r=0·588$, adrenaline $r=0·10$, both NS).

## Discussion

Alpha adrenergic stimulation has been shown to modulate coronary artery tone in dogs and patients with ischaemic heart disease.[8-10] $\text{Alpha}_2$ adrenoreceptors play an important role in the coronary vasoconstriction elicited by sympathetic nerve stimulation and in regulating the tone of both large and small coronary arteries.[9] Thus alterations in $\alpha_2$ adrenoreceptors might affect the coronary artery tone. In patients with symptomatic angina Weiss *et al* found a decrease in platelet $\alpha_2$ adrenoreceptor number that did not correlate with plasma catecholamine concentrations.[2] These findings raise the possibility that $\alpha_2$ adrenoreceptor abnormalities may be associated with the pathogenesis of angina. There is, however, little information on the changes in $\alpha_2$ adrenoreceptors in myocardial infarction. We found that soon after infarction the number of platelet $\alpha_2$ adrenoreceptors was significantly lower than it was one month later. There was no alteration in affinity. This decrease in receptor number soon after infarction was accompanied by an increase in the plasma catecholamine concentrations.

In an experimental study plasma catecholamines increased rapidly within one minute of coronary occlusion.[11] This increase was considered to reflect enhanced release of noradrenaline from the postganglionic sympathetic nerve endings in the heart.[12] Adrenaline secretion from the adrenal medulla was reflexly induced by stimulation of cardiac receptors at the site and the boundary of the infarct.[12] The increase in plasma catecholamine concentrations was also demonstrated early in myocardial infarction in a previous clinical investigation.[13] In the present study, catecholamine concentrations were significantly raised 6·6 (3 3) hours after infarction. The increase in our study, however, was less pronounced than that observed in previous investigations.[12 13] This might be due to our excluding patients with cardiogenic shock or severe heart failure, which are both conditions that enhance sympathoadrenal responses.[13]

Receptor down regulation is believed to occur when the cell is exposed for some time to higher concentrations of an agonist. The results of experimental studies of down regulation of platelet $\alpha_2$ adrenoreceptor are controversial.[14 15] Previous clinical studies found an inverse relation between plasma catecholamine concentrations, especially noradrenaline concentrations, and the number of $\alpha_2$ adrenoreceptors in various conditions such as phaeochromcytoma,[16 17] congestive heart failure,[18] and idiopathic orthostatic hypotension.[16] This suggests agonist induced down regulation as a possible underlying mechanism. Our results resemble these clinical investigations. The correlation between changes in the receptor number and catecholamine concentrations was not, however, statistically significant. Furthermore, the affinity of the receptor for catecholamines is much higher than the ranges of physiological concentrations.[19] Therefore, it appears unlikely that down regulation of platelet $\alpha_2$ adrenoreceptor occurs in vivo.

Some unknown mechanisms other than down regulation may be involved in the modulation of the receptor number. Further investigations are necessary to clarify the mechanisms which regulate $\alpha_2$ adrenoreceptor in vivo. In any event this decrease in the receptor number when catecholamine concentrations are raised during the early phases of acute infarction may be beneficial because it may moderate catecholamine induced reaction such as vasoconstriction.

We thank Mr Daniel Mrozek for reviewing our paper. This work was supported in part by grants for prostaglandin research for cardiovascular diseases from the Ministry of Health and Welfare; from the Ministry of Education, Science, and Culture, Tokyo, Japan; and the Suzuken Memorial Foundation and Mochida Memorial Foundation.

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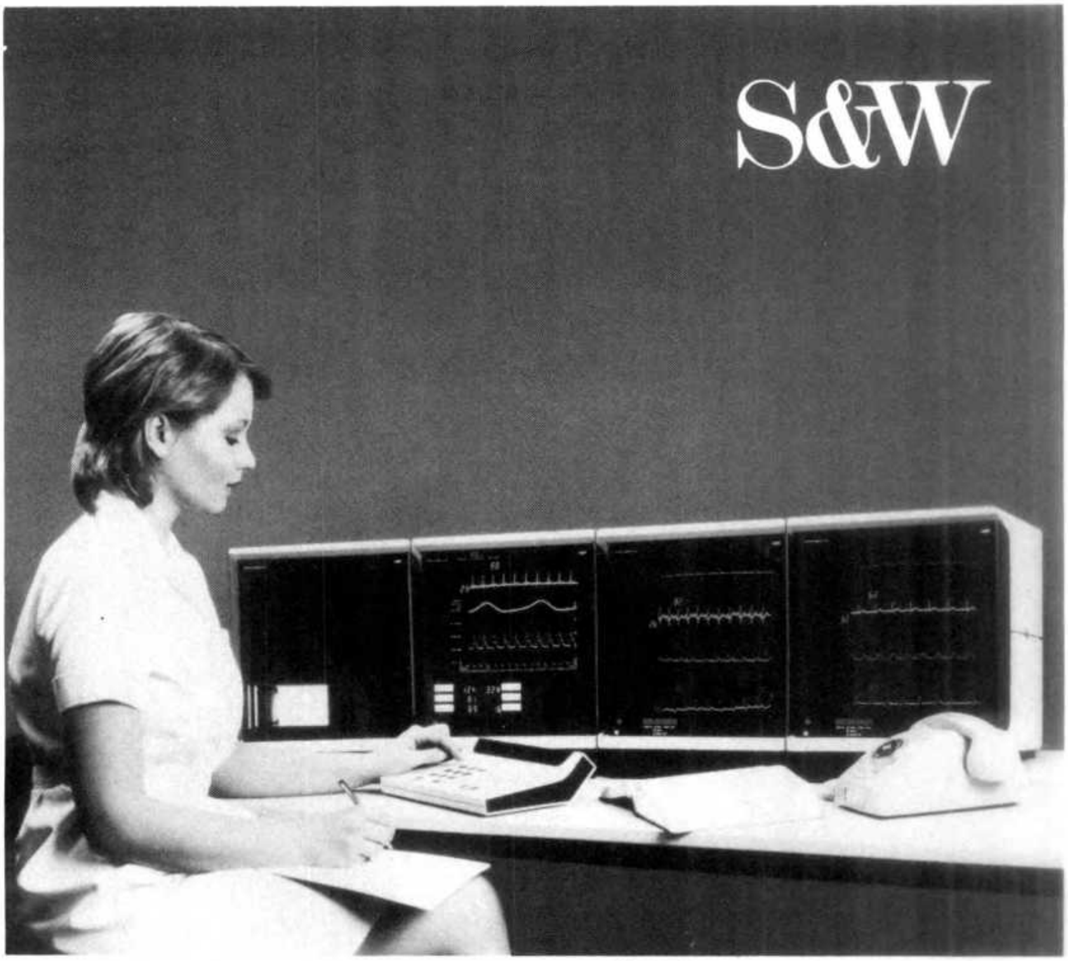

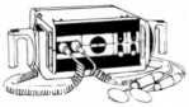
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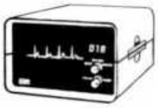
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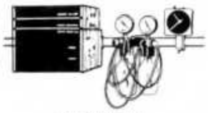
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*Br Heart J* 1986; 55: 439–45

# Factors determining symptoms in heart failure: comparison of fast and slow exercise tests

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SUMMARY Factors determining the symptoms of breathlessness and fatigue in patients with congestive heart failure were investigated by comparing the response to slow and fast exercise. Symptom limited oxygen consumption (maximal); minute ventilation, mean pulmonary capillary wedge pressure; and arterial blood gases, pH, and lactate concentrations were measured during treadmill exercise using a slow protocol in 25 men (age 34–67 years) with congestive heart failure (New York Heart Association class II-III). Ten of these patients were also exercised according to a rapid protocol. Exercise was terminated by fatigue in 23/25 patients after the slow test and by breathlessness in all patients after the rapid test. Exercise capacity (maximal oxygen consumption and exercise duration) was not related to resting or exercise pulmonary capillary wedge pressure or the change in pulmonary capillary wedge pressure during exercise, nor was there any difference in pulmonary capillary wedge pressure at the end of exercise within individuals between the fast and slow tests. Minute ventilation was greater (51 *vs* 43 l/min), peak exercise lactate concentration higher (3·7 *vs* 2·2 mmol/l), and the change in pH from the resting state was greater (0·06 *vs* 0·02) during the rapid test than during the slow test. The sensation of breathlessness in congestive heart failure is not simply related to raised pulmonary capillary wedge pressure, but may in part be due to stimulation of peripheral chemoreceptors in response to metabolic acidosis.

The cause of exercise intolerance in congestive heart failure is poorly understood. Patients treated with diuretics are limited more by fatigue than by breathlessness. Several studies have suggested that fatigue is related to an inadequate oxygen supply to skeletal muscle,[1-3] because during exercise patients with heart failure have a reduced cardiac output, an early increase in lactate concentration, and augmented limb oxygen extraction.[3] Common experience suggests that untrained normal subjects performing rapid exercise (for example running) often stop because of breathlessness, whereas when they exercise slowly (for example walking) they stop because of fatigue. In this study we have investigated whether the response to exercise in patients with congestive heart failure is similar, and if so whether differences in the metabolic, haemodynamic, and ventilatory responses to two forms of exercise can explain the variable sensations of breathlessness and fatigue.

## Patients and methods

### STUDY GROUP

Patients were eligible for the study if they had stable symptomatic heart failure for more than three months with exercise intolerance due to fatigue or dyspnoea. In addition the patients we studied had radiological evidence of cardiomegaly and left ventricular ejection fraction <45% on radionuclide or echocardiographic investigation. Twenty five men (mean age 50 years (range 34–67)) entered the study. The cause of heart failure was coronary artery disease in 15, dilated cardiomyopathy in eight, and hypertensive heart disease in two. Six patients were in class II and 19 in class III of the New York Heart Association classification. Patients were excluded if they had myocardial ischaemia or ventricular arrhythmias on exercise testing, obstructive valvar heart disease, pulmonary disease (documented by pulmonary function tests), or an inability to exercise for any reason other than dyspnoea or fatigue.

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Accepted for publication 11 February 1986

### PROTOCOL

To familiarise the patient with the exercise protocols, rapid and slow exercise tests were each performed twice in the two days before the study. Exercise was performed on a treadmill. Stages 1–4 consisted of treadmill speeds of 1, 1·5, 2, and 2·5 mph on the level. Stages 4–9 consisted of a treadmill speed of 2·5 mph and gradients of 2·5, 5, 7·5, 10, and 12·5%. In the slow exercise protocol stages lasted 6 min. The rapid exercise protocol consisted of a sudden increase in workload from rest to that level of exercise at which exercise stopped during the practice slow exercise tests. The patient was maintained at that workload for 3 min. The workload was then increased in stages every 2 min. We have previously shown that after a change in workload, oxygen consumption reaches 95% and 100% of the steady state value within 2 and 3 minutes respectively.[4]

A Swan-Ganz catheter was inserted into a subclavian vein under local anaesthesia and advanced into the pulmonary artery and a TF14 catheter was inserted into the brachial artery under local anaesthesia. All patients were exercised on the slow protocol. Ten patients were exercised on the slow and rapid protocol in a randomised order on the same day. The second exercise test was performed 4 h after the first test. Oxygen consumption, carbon dioxide production, and minute ventilation were determined at rest and during exercise by a mass spectrometer (Airspec 200 MGA) and an online computer as previously described.[4] Measurements were made every second and results were averaged over a 30 s period.

The anaerobic threshold was determined noninvasively from a graph of oxygen consumption against carbon dioxide production. A straight line of best fit was drawn through all points below 50% of maximal oxygen consumption attained. The anaerobic threshold was recorded as the level of oxygen consumption at which subsequent points began to deviate from this line. This technique provides results comparable to those obtained by graphical analysis with a computer.[4] Pulmonary artery wedge pressure was recorded at end expiration and pulmonary artery and arterial blood samples were obtained (for the determination of oxygen saturation and lactate concentration) at rest, at the end of each stage of exercise, and at maximal exercise. Mean and phasic arterial blood pressures were recorded continuously.

Arterial blood for lactate determination was deproteinised with cold perchloric acid and assayed by a spectrophotometric technique. Oxygen saturation of blood was determined by a reflectometer (American Optical Corporation). Haemoglobin concentration was measured by a Coulter counter. Blood oxygen content was calculated by multiplying haemoglobin concentration by 1·34 (ml/g haemoglobin) and by per cent saturation. Arteriovenous oxygen difference was calculated as the arterial oxygen content minus pulmonary artery oxygen content. Cardiac output was calculated by the Fick principle as oxygen consumption divided by arteriovenous oxygen difference. This method has been validated against the thermodilution technique.[5]

### REPRODUCIBILITY

Measurement of maximal oxygen consumption and anaerobic threshold and plasma lactate concentration has been shown to be reproducible.[6] The reproducibility of cardiac output and pulmonary capillary wedge pressure was assessed in five patients who performed two slow exercise tests within a 24 hour period. There was less than 12% variability in the measurement of cardiac output and pulmonary capillary wedge pressure recorded during the two exercise tests in the same patient.

### STATISTICAL METHODS

Data are expressed as mean (SEM) unless otherwise stated. Statistical analysis was performed by paired Wilcoxon test for paired data and by linear regression.

## Results

All patients were taking diuretics. The mean dose of frusemide was 45 mg for those patients in New York Heart Association class II and 110 mg for those in class III. Vasodilator treatment included captopril (n=6) and nitrates (n=5). Four patients, all of whom were in atrial fibrillation, were taking digoxin.

### EXERCISE CAPACITY AND HAEMODYNAMIC RESPONSE TO SLOW EXERCISE

Exercise testing was completed without incident in all patients. Exercise was terminated by fatigue in 18 patients and fatigue and breathlessness in five patients. Only two patients claimed that they stopped because of severe breathlessness alone.

Maximal oxygen consumption (ml/kg/min) for patients in New York Heart Association class II was 19 (1·7), and class III 13 (0·9), which is considerably below the normal range for this age group.[7] Values recorded are symptom limited maximal oxygen consumption. It was not possible to demonstrate a genuine plateau of oxygen consumption with increasing workload because patients stopped exercise before this point was reached.

The haemodynamic and ventilatory changes were analysed by regression analysis. There was no correlation between resting, maximal, or change in pul-

Table 1 *Haemodynamic and ventilatory changes during the slow exercise protocol in patients with heart failure*

| *Patient* | *$\dot{V}O_2$ max (ml/kg/min)* | *Exercise duration (min)* | *PCWP (mm Hg)* | | | *Cardiac index (l/min/mm²)* | |
|---|---|---|---|---|---|---|---|
| | | | *Rest* | *Exercise* | *Change* | *Rest* | *Exercise* |
| 1 | 25 | 64 | 4 | 18 | 14 | 2·1 | 10 |
| 2 | 17 | 34 | 24 | 30 | 6 | 1·7 | 4·1 |
| 3 | 22 | 64 | 17 | 30 | 13 | 2·4 | 6·6 |
| 4 | 12 | 22 | 20 | 26 | 6 | 1·5 | 3·1 |
| 5 | 11 | 33 | 22 | 29 | 7 | 2·2 | 3·3 |
| 6 | 13 | 34 | 13 | 28 | 15 | 1·9 | 3·0 |
| 7 | 14 | 46 | 10 | 20 | 10 | 2·2 | 4·5 |
| 8 | 20 | 17 | 16 | 36 | 20 | 2·6 | 5·9 |
| 9 | 11 | 24 | 22 | 23 | 1 | 2·8 | 3·5 |
| 10 | 12 | 17 | 12 | 25 | 13 | 2·4 | 3·3 |
| 11 | 11 | 18 | 10 | 24 | 14 | 2·2 | 3·3 |
| 12 | 12 | 16 | 25 | 29 | 4 | 1·7 | 2·8 |
| 13 | 14 | 44 | 25 | 42 | 17 | 2·2 | 3·9 |
| 14 | 11 | 17 | 10 | 21 | 11 | 1·5 | 3·7 |
| 15 | 18 | 40 | 10 | 21 | 11 | 3·4 | 7·0 |
| 16 | 17 | 40 | 14 | 23 | 9 | 3·5 | 6·5 |
| 17 | 21 | 59 | 8 | 16 | 8 | 1·6 | 4·6 |
| 18 | 14 | 34 | 12 | 42 | 30 | 2·1 | 4·3 |
| 19 | 19 | 26 | 8 | 13 | 5 | 2·7 | 4·7 |
| 20 | 15 | 24 | 15 | 28 | 13 | 1·7 | 3·0 |
| 21 | 10 | 17 | 32 | 32 | 0 | 1·7 | 2·7 |
| 22 | 10 | 19 | 34 | 36 | 2 | 1·9 | 3·4 |
| 23 | 22 | 17 | 22 | 30 | 8 | 2·0 | 5·5 |
| 24 | 13 | 17 | 11 | 18 | 7 | 2·0 | 5·0 |
| 25 | 16 | 30 | 14 | 44 | 30 | 2·2 | 5·6 |
| Mean | 15·3 | 31 | 16 | 27 | 11 | 2·2 | 4·5 |
| SD | 4·3 | 15 | 7 | 8 | 7·3 | 0·5 | 1·7 |

$\dot{V}O_2$ max, maximal oxygen consumption, PCWP, pulmonary capillary wedge pressure.

monary capillary wedge pressure and maximal oxygen consumption ($r=-0{\cdot}38$. $r=-0{\cdot}19$, and $r=0{\cdot}12$ respectively) (Fig. 1) or exercise duration ($r=-0{\cdot}36$, $r=0{\cdot}16$, $r=-0{\cdot}15$). In contrast, maximal cardiac index on exercise did correlate with maximal oxygen consumption and exercise duration ($r=0{\cdot}77$, $p<0{\cdot}0001$ and $r=0{\cdot}60$, $p<0{\cdot}001$ respectively). Cardiac index at rest did not correlate with maximal oxygen consumption or exercise duration ($r=0{\cdot}21$, $r=0{\cdot}18$ respectively) (Table 1).

### VENTILATORY HAEMODYNAMIC AND METABOLIC RESPONSE TO FAST EXERCISE

Ten patients exercised by both the slow and fast exercise protocols, so that within patient comparison of responses to these tests was possible. All 10 patients were among those who stopped exercise on the slow protocol because of fatigue. On the fast exercise protocol these patients stopped exercise because of severe breathlessness. Maximal oxygen consumption correlated with maximal cardiac index ($r=0{\cdot}6$, $p<0{\cdot}05$) with maximal pulmonary capillary wedge pressure (Fig. 2) ($r=-0{\cdot}1$). Patients were able to exercise to a greater workload on the fast test (mean of 2·2 stages further than on the slow test). Minute ventilation at peak exercise was significantly higher during the fast test than during the slow test (51 *vs* 43 l/min, $p<0{\cdot}01$). Furthermore the mixed expired oxygen concentration at peak exercise was significantly greater during the rapid protocol than during the slow protocol (17·6 *vs* 17·0%, $p<0{\cdot}01$), suggesting that the sensation of breathlessness was associated with a greater degree of hyperventilation. Maximal oxygen consumption was greater at the end

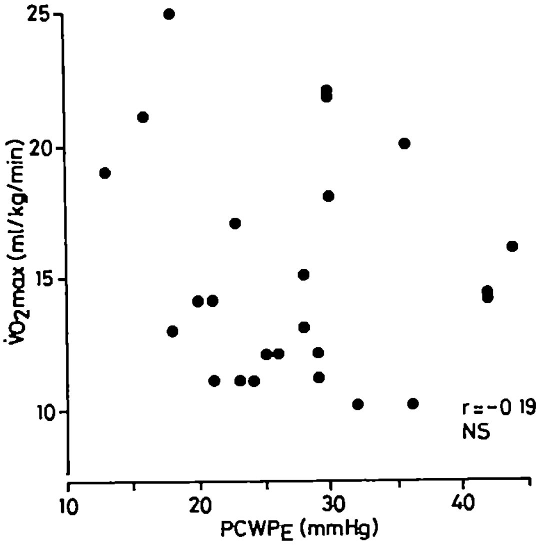

Fig. 1 *Relation between maximal oxygen consumption ($\dot{V}O_2$ max) and maximal pulmonary capillary wedge pressure ($PCWP_E$) during the slow exercise test.*

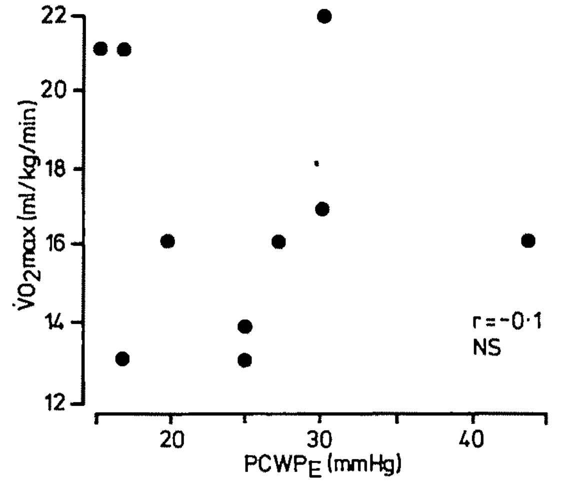

Fig. 2 *Relation between maximal oxygen consumption ($\dot{V}O_2$ max) and maximal pulmonary capillary wedge pressure (PCWP$_E$) during the rapid exercise test.*

of the fast protocol than at the end of the slow protocol (16·8 *vs* 14·9 ml/kg/min, $p<0·01$), as was anaerobic threshold (12 *vs* 11 ml/kg/min, $p<0·01$). Mean blood pressure at peak exercise was the same during the slow and fast protocols. Though the reasons for stopping exercise were different in the two tests the mean pulmonary capillary wedge pressure in the patients at peak exercise was the same in the two tests ($p<0·3$).

Arterial blood lactate concentration at peak exercise was higher and the change in arterial blood pH from the resting stage was greater during the fast test than during the slow test (3·7 *vs* 2·2 mmol/l, $p<0·01$; 0·06 *vs* 0·02, $p<0·01$) (Table 2).

## Discussion

Patients with congestive heart failure frequently have limited exercise capacity because of fatigue and breathlessness. The present study has demonstrated that the symptom that ultimately terminates exercise depends on the type of exercise performed. Patients exercising on the fast protocol were stopped by breathlessness, yet when they exercised on the slow protocol fatigue was the limiting factor. We have obtained a similar result in a small pilot study of a different group of patients.[8]

The sensation of breathlessness was accompanied by objective changes in ventilatory gas exchange. Minute ventilation and mixed expired oxygen concentration were greater during the rapid test than during the slow exercise test, suggesting that the symptom of breathlessness was associated with a greater hyperventilatory response.

Many mechanisms have been put forward to account for breathlessness in patients with heart failure. Patients with congestive heart failure have an increased physiological and anatomical dead space.[9 10] It has been suggested that the hyperventilatory response seen in these patients occurs because more respiratory effort is required to ventilate the dead space and maintain eucapnia.[10] Comparisons made within patients indicate that this effect is unlikely to account for the different symptoms during slow and fast exercise tests.

Juxtapulmonary capillary receptors (J receptors) may be activated by lung stiffening, such as that which occurs with the accumulation of interstitial fluid, and this can result in tachypnoea and the sensation of breathlessness.[11] Decreased lung compliance, however, does not correlate with the degree of

Table 2 *Comparative haemodynamic, ventilatory, and metabolic changes during the rapid and slow exercise tests in patients with chronic heart failure*

| *Patient* | *$\dot{V}O_2$ max (ml/kg/min)* | | *Anaerobic threshold (ml/kg/min)* | | *Cardiac index (l/min/m$^2$)* | | *Systemic BP (mm Hg)* | | *PCWP$_E$ (mm Hg)* | | *Minute ventilation (l/min)* | | *Δ Arterial pH* | | *Δ PaCO$_2$ (mm Hg)* | | *Lactate (mmol/l)* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Slow* | *Fast* | *Slow* | *Fast* | *Slow* | *Fast* | *Slow* | *Fast* | *Slow* | *Fast* | *Slow* | *Fast* | *Slow* | *Fast* | *Slow* | *Fast* | *Slow* | *Fast* |
| 1 | 19 | 21 | 14 | 15 | 4 7 | 4 7 | 95 | 102 | 13 | 15 | 35 | 42 | 0 05 | 0·1 | +1 | 0 | 2·2 | 3 8 |
| 2 | 20 | 21 | 13 | 14 | 5 9 | 5 5 | 93 | 93 | 36 | 30 | 63 | 77 | 0 02 | 0 06 | −1 | 0 | 2·4 | 3 9 |
| 3 | 14 | 16 | 11 | 11 | 4·4 | 4 5 | 96 | 96 | 20 | 20 | 41 | 46 | 0 02 | 0·08 | 0 | −3 | 2·5 | 4 2 |
| 4 | 11 | 13 | 8 | 9 | 3 7 | 4 2 | 69 | 75 | 21 | 17 | 37 | 49 | 0 04 | 0·06 | +4 | +1 | 2 6 | 3 5 |
| 5 | 21 | 21 | 19 | 19 | 4 6 | 4 5 | 86 | 88 | 16 | 17 | 49 | 49 | 0·03 | 0 03 | −2 | −2 | 2·3 | 4 2 |
| 6 | 11 | 14 | 10 | 11 | 3 3 | 3 5 | 70 | 71 | 25 | 25 | 39 | 49 | 0 02 | 0·04 | 0 | 0 | 1 0 | 2 5 |
| 7 | 13 | 16 | 10 | 11 | 3 0 | 3 7 | 108 | 100 | 28 | 27 | 41 | 52 | 0 03 | 0·04 | −5 | −2 | 2·3 | 5 1 |
| 8 | 14 | 16 | 10 | 11 | 4 3 | 5 5 | 104 | 106 | 42 | 44 | 47 | 49 | 0·00 | 0 07 | −4 | 0 | 2 5 | 3 5 |
| 9 | 11 | 13 | 10 | 11 | 3 3 | 3·5 | 83 | 74 | 28 | 25 | 36 | 45 | 0·01 | 0 05 | −1 | −2 | 1 7 | 3 0 |
| 10 | 15 | 17 | 11 | 12 | 3 0 | 3·3 | 69 | 67 | 30 | 30 | 41 | 48 | 0·02 | 0 03 | +1 | −4 | 2·3 | 3 1 |
| Mean | 15 | 17 | 11 | 12 | 4 0 | 4 3 | 87 | 87 | 26 | 25 | 43 | 51 | 0·02 | 0 06 | −1 | −1 | 2 2 | 3 7 |
| SE | 1 | 1 | 1 | 1 | 0 3 | 0 2 | 4 | 4 | 3 | 3 | 3 | 3 | 0·01 | 0 01 | 0 | 0 | 0 1 | 0 2 |
| p | <0·01 | | <0·01 | | NS | | NS | | NS | | <0 01 | | <0 01 | | NS | | <0·01 | |

$\dot{V}O_2$ max, maximal oxygen consumption; Δ Arterial pH, change in arterial pH from rest at end of exercise; PCWP$_E$, maximal pulmonary capillary wedge pressure; Δ PaCO$_2$, change in partial pressure of arterial carbon dioxide from rest at the end of exercise; BP, blood pressure.

dyspnoea[12-14] and only small increases in pulmonary blood volume and pulmonary extravascular fluid have been demonstrated in patients with left ventricular dysfunction.[15] In the present study there was no correlation between resting or maximal pulmonary capillary wedge pressure and maximal oxygen consumption in patients exercised on the slow protocol; this accords with the studies by Franciosa *et al.*[16 17] Furthermore, there was no difference in maximal pulmonary capillary wedge pressure at the end of the slow and fast exercise tests. These findings suggest that a high pulmonary capillary wedge pressure does not limit exercise tolerance and is not the major factor responsible for the sensation of breathlessness in patients with congestive heart failure. The interpretation based on this data should not be applied to patients with acute onset of left ventricular failure where a high left atrial pressure results in pulmonary oedema and breathlessness.

If a respiratory cause was primarily responsible for the exercise limitation in congestive heart failure, a fall in arterial oxygen saturation would be expected. We and others have shown normal arterial oxygen saturation during exercise in these patients.[6 18]

An alternative mechanism may be operating during the metabolic changes that occur during exercise. Plasma lactate concentration is increased primarily as a consequence of an inadequate supply of oxygen to metabolising tissue,[19] with resultant anaerobic metabolism. Skeletal muscle blood flow is reduced in patients with congestive heart failure and this accounts for the early appearance of lactate in the femoral vein on exercise.[3] Fast twitch muscle fibres produce lactate despite an adequate supply of oxygen[20] and they are recruited for short bursts of strenuous muscle activity. A reduction of blood flow to the liver and diminished hepatic metabolism may contribute to the rise of blood lactate concentration. Rapid exercise will thus result in a greater rate of production of lactate which exceeds its rate of metabolism by the liver; hence the higher blood lactate concentration that was seen at the end of the fast protocol.

Lactate is buffed by bicarbonate in the blood producing carbon dioxide in excess of that resulting from aerobic metabolism. Arterial carbon dioxide tension was unchanged from the resting value at the end of both exercise protocols, yet arterial blood pH was significantly lower at the end of the fast test than at the end of the slow test; this is consistent with the greater rise in plasma lactate concentration seen during this test.

The ventilatory response in normal people during exercise may be related to feedback loops that monitor the changes in arterial pH and carbon dioxide tension and depend on intact carotid body receptors.[21 22] The ventilatory response to exercise and exercise capacity can be modified by alterations of pH and carbon dioxide tension in arterial blood.[23] The present study shows that the sensation of breathlessness was associated with a rapid rise in plasma lactate concentration and fall in arterial pH.

Such observations do not necessarily imply cause and effect nor that the hyperventilatory response is solely dependent on the metabolic changes in the blood on exercise. Patients with McArdle's disease cannot produce lactic acid yet they hyperventilate on exercise.[24] It has been suggested that the hyperventilatory response in these patients may be induced by skeletal muscle pain.[25] It is unlikely that a local stimulus in muscle mediated by neural mechanisms[26] is solely responsible for the sensation of breathlessness in normal people and patients with congestive heart failure, because a hyperventilatory response has been shown to occur in patients with spinal transection.[27] The present results are consistent with the idea that the sensation of breathlessness that occurs in patients with congestive heart failure during rapid exercise is in part the consequence of the rapid rise in blood lactate concentration and fall in pH that stimulate the hyperventilatory response.

Fatigue is the second major symptom of patients with heart failure. This study demonstrates that exercise tolerance in congestive heart failure is related to maximal cardiac output during exercise. Wilson *et al* demonstrated that patients with congestive heart disease stopped exercise because of fatigue when a critical level of muscle underperfusion occurred and they concluded that the low maximal exercise capacity of patients with congestive heart failure was the result of impaired nutritive flow to skeletal muscle.[3] Though the results of this study accord with that idea, other factors may be relevant. Most patients stopped exercise on the slow protocol because of fatigue. When 10 of these patients were exercised on the fast protocol, however, they stopped exercise at significantly higher cardiac outputs and maximal oxygen consumption, yet with the same mean arterial blood pressure, than when they were exercised on the slow protocol.

There are two explanations for this unexpected finding. The sensation of fatigue in congestive heart failure is not dependent solely on impaired nutritive flow to exercising muscle. Rise in body temperature, boredom, and lack of motivation may have ended the exercise test prematurely. Alternatively, prolonged exercise may be associated with an increase in skin blood flow to offset the rise in body temperature and maintain thermoregulatory control. This would divert blood from skeletal muscle and lead to the earlier development of anaerobic metabolism and a fall in intracellular pH as lactic acid accumulates within the cell. Presumably the rate of lactate production is nearly matched by the rate of lactate clearance and hence there is only a small rise in blood lactate concentration. Intracellular acidosis is closely related to and may be partly responsible for muscle fatigue.[28-30]

We have demonstrated that the design of an exercise protocol is important when assessing the maximal exercise capacity of patients with congestive heart failure. Though a steady state may not be reached with protocols with stages of short duration,[31] if prolonged exercise testing is used to ensure a steady state at each stage of the exercise test symptom limited maximal oxygen consumption, anaerobic threshold, and maximal cardiac output may be underestimated. Similar observations were recently made by Buchfuhrer *et al* in normal people; as a result they suggested selecting work rate increments to bring the subjects to the limit of their exercise tolerance in about 10 minutes.[32] Further studies are required to evaluate the best exercise protocol for studying exercise capacity of patients with heart failure; the present study suggests that short exercise protocols with rapid increases in workload are desirable.

This study has shown that the symptoms limiting exercise tolerance in patients with congestive heart failure depend on the type of exercise performed and that such symptoms are independent of changes in pulmonary capillary wedge pressure. Metabolic changes may contribute to the sensation of breathlessness during rapid forms of exercise. Symptom limited maximal oxygen consumption and peak cardiac output recorded during exercise are affected by the length of the exercise protocol. The design of exercise protocols for the assessment of patients with congestive heart failure must take these factors into account.

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# Analysis of interobserver and intraobserver variation of interpretation of the echocardiographic and Doppler flow determination of cardiac output by the mitral orifice method

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SUMMARY The variability of the interpretation by two individuals of a combined echocardiographic and Doppler method of calculating output was studied in 30 normal adults. In each subject three separate cardiac cycles were recorded to calculate maximal mitral valve orifice, the ratio of mean to maximal mitral valve leaflet separation, and the mean flow velocity through the mitral valve. The recordings were digitised twice by two independent observers. Estimates of cardiac output ranged from 3·2 to 8·1 l/min. Analysis of variance showed that interobserver and intraobserver variability for these measurements was 5·8% and 6·1% respectively.

It is concluded that the reproducibility for interpreting this non-invasive method is adequate for clinical use in adults with cardiac outputs within the normal range.

A combined echocardiographic and Doppler flow technique that assesses blood flood through the mitral valve has been used to estimate cardiac ouput in animal models[1 2] and in patients.[3 4] We have analysed the variability of intraobserver and interobserver results when estimates of flow through the mitral orifice were used to calculate cardiac output in normal adults.[1]

## Patients and methods

We studied thirty four normal adults. Four were subsequently excluded because of poor quality echocardiograms. The mean age of the remaining 30 was 32 (16–52 years) (15 men, 15 women).

Echocardiograms and pulsed Doppler recordings were made on a Honeywell Ultra-imager with a 3·5 MHz mechanical transducer. Three prints of stop frame echocardiographic video images of three separate cardiac cycles were used to estimate the maximum mitral valve orifice (from parasternal short axis views).

We obtained M mode recordings of the mitral valve at the same level through the leaflets as the cross sectional study. Again, three cardiac cycles were recorded. Then with the transducer positioned on the cardiac apex a pulsed Doppler sample volume was set to a length of 1 cm and positioned just below the mitral leaflets. The sample lies parallel to ventricular inflow (or was estimated to be no more than 15° off parallel). Doppler flow was recorded for three cycles on hard copy at a paper speed of 50 mm/s. M mode recordings were obtained at the same recording speed.

One investigator obtained all the echocardiographic images and Doppler recordings from resting and haemodynamically stable subjects. On two occasions two observers independently and blindly calculated mitral valve area from hard copies of real time and M mode traces of the three cycles.

For technical reasons, which were specific to our computer system digitising pad, the Doppler flow curves were traced on to plastic transparency from the hard copy and the transparencies were digitised.

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Accepted for publication 21 January 1986

The densest part of the velocity trace was taken as the modal velocity.

A third observer independently and blindly performed the computer digitisation of the transparency traces of the modal velocities of the three cycles. The computer system calculated the area under each curve to determine the mean velocity of transmitral flow for each cycle.

The maximum mitral area was estimated from tracings on transparencies of the real time stop frame image (both observers produced two tracings for each cycle). The line of the trace followed the inner contour of the mitral leaflets. The transparencies were then digitised independently and blindly by the third observer to calculate maximal mitral valve orifice for the three recorded cycles. Mean to maximal mitral leaflet separation was calculated for the three beats from the M mode traces. The mean mitral maximal area was multiplied by the ratio of the mean to maximal valve leaflet separation to give an effective mean diastolic cross sectional orifice area for the mitral valve (this ratio is said to correct for variations in mitral valve orifice size during diastole).[1] The two observers traced the anterior and posterior mitral leaflets on the M mode trace. They did this twice for the three recorded cycles. The tracings were digitised blindly by the third observer.

The mean:maximal mitral orifice ratio was calculated from the formula—$A/l \times h$, where A is the area of the anterior and posterior mitral leaflets on M mode; h is the maximal leaflet separation; and l is the duration of leaflet separation (diastole). Cardiac output was calculated using the formula: $CO = (V\ CSA\ 60)/\cos\theta$; where CO is cardiac output (l/min); V is mean velocity throughout the entire cardiac cycle uncorrected for angle (cm/s), calculated as the mean of the three cycles and of the four measurements performed by the two observers; CSA is effective mean diastolic mitral valve orifice area corrected for diastolic variations (cm$^2$), determined by multiplying the cross sectional maximal mitral valve orifice area by the ratio of mean:maximal mitral leaflet separation on the M mode recording. All the measurements were the mean of the three cycles and of the four determinations of the two observers; $\cos\theta$ is the cosine of the angle between the Doppler beam and blood flow. For the purpose of this study the $\cos\theta$ was assumed to be 1 for all calculations for the following reasons: (a) the purpose of the study was to analyse the interpretative reproducibility and not the effect of the angle $\theta$; (b) in 80% of our cases the angle was effectively 0 and all other sampling angles were less than 15°; (c) to simplify statistical analysis of the data by avoiding variables not strictly related to interpretative reproducibility; (d) a true correction would have to be performed in three planes and this would be impracticable and subjective.

Final results of cardiac ouput values are given as the mean of the four measurements obtained by the two observers.

### STATISTICAL ANALYSIS

Interobserver and intraobserver interpretative variability was calculated by analysis of variance. The variability was determined not only for cardiac output measurements, but also for each of the three factors included in the formula for calculating cardiac output (cross sectional echocardiographic measurements, M mode echocardiographic measurements, Doppler measurements) and beat to beat for each of the three beats used for the analysis.

The 30 cases were also arbitrarily divided into three groups on the basis of excellent quality recordings (15 cases), good quality recordings (10 cases), and fair quality recordings (five cases) to evaluate the possible influence of the quality of the recording on the final variability.

## Results

Calculated Doppler cardiac output values ranged from 3·2 to 8·1 l/min (mean 5·1 (1·3) l/min). The interobserver and intraobserver variability for cardiac ouput was 0·295 l/min (5·8%) and 0·310 l/min (6·1%) respectively.

Table 1 shows the interobserver and intraobserver variability for cross sectional measurements, M mode measurements, and Doppler measurements as well as beat to beat variability for the three groups of measurements. Table 2 shows the total interpretative variability for the cross sectional measurements, M mode measurements, and Doppler

Table 1 *Interobserver, intraobserver, and beat to beat variability*

| *Variability* | *Cross sectional* | | *M mode* | | *Doppler* | |
|---|---|---|---|---|---|---|
| | *cm$^2$* | % | *Units* | % | *cm/s* | % |
| Interobserver | 0·141† | 2·5 | 0·0085* | (1·6) | 0·53† | 1·8 |
| Intraobserver | 0·312 | 5·5 | 0·0175 | (3·3) | 1·57 | 5·5 |
| Beat to beat | 0·424† | 7·5 | 0·0147† | (2·8) | 1·22† | 4·3 |

*p = 0·01 compared with intraobserver variability
†p = 0·001 compared with intraobserver variability

Table 2 *Variation in the interpretation of cross sectional, M mode, and Doppler measurements on the basis of the quality of the recordings*

| *Quality* | *Cross sectional* | | *M mode* | | *Doppler* | |
|---|---|---|---|---|---|---|
| | *cm²* | % | *Units* | % | *cm/s* | % |
| Excellent (n=15) | 0·549* | 9 9 | 0 0245 | (4 9) | 2·36* | 8 2 |
| Good (n=10) | 0 677* | 11·0 | 0 0363 | (6 8) | 2 17 | 7·6 |
| Fair (n=5) | 0·566* | 10·5 | 0 0351 | (6 0) | 2 70* | 9 4 |

*p<0 001 compared with M mode (Fisher F test for variance).

measurements on the basis of the quality of the recordings.

## Discussion

We studied the variability of the interpretation of recorded data not variability due to the recording procedure. Both interobserver and intraobserver variability was close to 6%.

Real time, M mode, and Doppler measurements were associated with similar degrees of variability, although real time measurements tended to produce more variability and M mode less.

Although adult real time images are inherently less satisfactory than paediatric images, we found that provided the image was suitable for analysis, the difference in their grading was not a major factor in producing the variability (Table 2). Although the subjects in our study were clinically normal, image studies were unsatisfactory in four (12%) of them. Presumably the proportion of unacceptable recordings in ill patients in intensive care who may have had recent thoracic surgery will be much higher. Our subjects all had cardiac output values in the normal range. Whether or not similar reproducibility would be obtained in low output states has yet to be determined.

We have not entered into the debate on the preferred site for recording blood flow—that is the aorta or transmitral position—nor have we examined the assumption that the mitral orifice is circular in diastole.[3] We examined the suggestion that variability within and between interpretors can significantly influence the accuracy of measurement.[5] We found that in a small group of normal individuals the interpretative variability of analysing the echocardiographic and Doppler measurements required for mitral flow calculations was within clinically acceptable limits. A larger series incorporating a range of output states is needed to analyse further factors that may affect variability.

We thank Dr David Sahn, University of California Medical Centre, San Diego for help and advice.

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*Br Heart J* 1986; 55: 449–58

# Factors that influence the outcome of primary pulmonary hypertension

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SUMMARY Factors predicting life expectancy in primary pulmonary hypertension have not been well defined. Thirty four cases of primary pulmonary hypertension that had been followed up until death or for at least five years were reviewed retrospectively. Patients were divided into three groups: 18 patients who died within five years of presentation to hospital; 12 who survived more than five years; and four who improved and who lived for more than five years. The age at onset was similar in the three groups and, like symptoms and sex, did not predict life expectancy. Right heart failure during the course of the disease was associated with a poor outcome. Radiographic evidence of cardiac enlargement and evidence of right heart strain on electrocardiogram at presentation was also predictive of survival for < five years. Pulmonary arteriolar resistance was higher and cardiac output lower in those with the shortest survival times. There was no relation between pulmonary artery pressure and length of survival. Systemic resistance varied directly with pulmonary resistance and served to maintain systemic pressure. Presentation in or after pregnancy and patency of the foramen ovale were associated with longer survival. In four patients there was evidence of regression of the disease by cardiac catheterisation and lung histology.

Primary pulmonary hypertension is a heterogenous condition in which life expectancy varies widely.

Primary pulmonary hypertension is a rare disease. The condition was well known to Paul Wood and the clinical features were meticulously presented by him in 1952, but credit for the first full description is usually given to Dresdale *et al.*[1] The pathology was reviewed by Brenner in 1935. In 1970 Wagenvoort and Wagenvoort in their detailed multicentre study of lung histology put forward the criteria necessary for complete diagnosis.[2] The incidence is at most one in 200 of all cases of cardiac disease that go to catheterisation.[3 4]

There have been few follow up studies of sufficient size for valid conclusions to be reached on the factors predicting outcome.[3 5 6] The largest reviews have been multicentre ones,[2 5 7] or have been cases collected from published reports.[8] The identification of risk factors might provide a greater understanding of pathophysiology and ultimately help in treatment.

The haemodynamic, electrocardiographic, and chest *x* ray findings accompanying clinical deterioration have been reported,[3 5] but the relation of these changes to life expectancy has not. Right heart failure usually occurs with time. Some patients with primary pulmonary hypertension have a patent foramen ovale due to persistently raised right atrial pressure. There is experimental evidence that such a shunt can prevent sudden death.[9 10] We examined the prognostic importance of right heart failure and of the presence of a patent foramen ovale.

The influence of associated disease on outcome is uncertain. Pulmonary hypertension is found in association with various connective tissue disorders[11 12] in the absence of interstitial lung damage, but in most patients with pulmonary hypertension there is no evidence of another disease. The preponderance of females in both conditions is well

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Accepted for publication 6 January 1986

known.[2 3 5] Oral contraception[13 14] and pregnancy[15] have been linked with progressive pulmonary vascular disease—both to the apparent onset of primary pulmonary hypertension and to development of the Eisenmenger syndrome in ventricular septal defect. Presentation in right heart failure towards the end of pregnancy or post partum is well recognised and generally considered to carry a poor immediate and long term outlook.[15] This was not our experience. Finally, survival from time of presentation or onset of symptoms is variable[3 8] and reports of spontaneous regression have been rare[8 16 17] except after ingestion of anorectic drugs.[6] Regression may occur more frequently than supposed.

## Patients and methods

The records of all 34 patients with a diagnosis of primary pulmonary hypertension attending Hammersmith Hospital between 1961 and 1981 were traced. All of them had been followed until death or had survived for at least five years from the time of presentation to a hospital. Those who had been followed up for less than five years and who were still alive were not included in this series.

Pulmonary hypertension is deemed to be idiopathic when all known causes have been excluded. We believe that pulmonary perfusion must be assessed before idiopathic pulmonary hypertension can be diagnosed. In a retrospective series of patients with primary pulmonary hypertension in which lung histology was available, such investigations had not been universally applied, and most of those who were misdiagnosed had thromboembolic hypertension.[2] The criteria for diagnosis and the number of tests used were: right ventricular hypertrophy on the electrocardiogram in the absence of known cause (34); raised pulmonary artery pressure and normal capillary wedge or left ventricular filling pressure (34); pulmonary angiogram consistent with primary pulmonary hypertension (29); normal ventilation perfusion lung scan (25); consistent lung histology (5); M mode echocardiogram (13). No patient had taken oral contraceptives before presentation and none had been taking anorectic medication at any stage.

Seven patients had more than one cardiac catheterisation. All had had a ventilation perfusion scan or pulmonary angiogram, and most had had both. Nineteen of 25 perfusion lung scans were normal and six showed only minor perfusion abnormalities.[18 19] Pulmonary angiograms showed no evidence of pulmonary emboli. Lung histology was studied at necropsy. The M mode echocardiogram recordings had features consistent with idiopathic pulmonary hypertension in every case.[20]

Follow up was measured from the time of presentation to hospital and ranged from five to 28 years; follow up at Hammersmith Hospital was eight months to 14 years. Data were compiled from our records and those of the referring physicians. Details of the history, examination, electrocardiogram, and chest $x$ ray within the first six months of hospital attendance were available for every subject. Whenever findings were abnormal during this period they were recorded as being those at presentation. Further clinical details were obtained from the patient when possible. Overt right heart failure was defined as a combination of a raised jugular venous pressure, enlargement of the liver, and peripheral oedema. The resting electrocardiogram was analysed for right atrial strain, frontal axis, and evidence of right ventricular hypertrophy. The criteria for right ventricular hypertrophy were fulfilled if two or more of the following four conditions were met: R wave in $V1 > 0{\cdot}7\,mV$, S wave in $V1 < 0{\cdot}2\,mV$, sum of the amplitudes of the R wave in V1 and larger of the S waves in V5 or $V6 > 1{\cdot}05\,mV$, and R wave in $aVR > 0{\cdot}5\,mV$.[21] Right axis deviation was defined as a mean frontal QRS axis greater than $+90°$. Chest $x$ rays were assessed by one observer and a radiologist aware of the likely diagnosis, but without knowledge of individual clinical courses. Analysis was subjective and for right ventricular enlargement was based on the lateral view. For the size of the main pulmonary artery, the posterior anterior projection was used. No patient had radiologically detectable interstitial lung disease.

Further investigations, especially cardiac catheterisations, were often performed after the first six month period. Catheterisation was always carried out with the patient in the fasting supine resting state. Assumed oxygen consumption was used to calculate cardiac output in all but three cases. Existence of a right to left shunt at atrial level was based on catheter patency and desaturation of left atrial blood. We excluded subjects in whom this was secondary to an atrial septal defect rather than a patent foramen ovale.[22]

Patients were divided into three groups according to their clinical course: group I, 18 who died within five years of presentation; group II, 12 patients who survived for longer than five years; and group III, four patients in whom there was evidence of regression. The survival time was examined in relation to associated conditions and to the haemodynamic data in an attempt to identify significant prognostic factors. One tailed Fisher's exact probability test and Student's $t$ test were applied where appropriate. Linear regression analysis and Spearman rank correlation coefficient were also used.[23] Statistical significance was taken as $p < 0{\cdot}05$.

## Results

There was no relation between age at presentation and mean survival (Table 1). The ratio of females to males was significantly lower for those aged $\geqslant 45$ at presentation than for those $<45$ at presentation ($p<0\cdot01$). Twenty six of the 34 patients studied were female. The most frequent symptoms when the patients were first seen at hospital were breathlessness (100%), syncope or dizziness (50%), palpitation (11·8%), and exertional chest pain (5·9%). The mean age at onset of symptoms was 33, 30, and 27 years, for groups I, II, and III respectively. Seven were children aged $<16$; the youngest was 18 months old.

Table 2 summarises the initial clinical features of the three groups. Right ventricular failure at presentation was significantly more common in group I than in group II ($p<0\cdot05$). Ascites was present in 50% of those in failure. All patients in group I eventually developed signs of right heart failure, and no deaths were sudden. Only one patient in group II presented in right heart failure, but seven subsequently developed this complication and five of them died. Two of this group are alive; both have a patent foramen ovale. Clinical evidence of right ventricular failure was examined in relation to chest *x* ray and electrocardiographic findings. Only right ventricular enlargement and two of the three chosen electrocardiographic features of ventricular overload were present to a significantly greater degree in those who died within five years than in those who did not. All these features remained unchanged or progressed in the patients of groups I and II who died. There was little response to diuretics and only one patient was treated with digoxin. All were put on warfarin and none was treated with vasodilators. In contrast, two of the four patients in group III were originally in heart failure; one recovered (case 1) and in another (case 2) there was a long period of stable congestive heart failure.

Table 3 shows haemodynamic data at rest. There were no significant differences between the three groups for mean right atrial pressure, right ventricular filling pressure, and peak systolic and mean pulmonary artery pressure, although all these variables were higher in groups I and II than in group III. Left ventricular filling pressure (measured directly in six) was greater and cardiac output lower in those who survived $<5$ years. Pulmonary arteriolar resistance and systemic vascular resistance were lower in those in whom the disease regressed than in those who died within five years of presentation. There was a direct linear relation between pulmonary arteriolar resistance and systemic resistance ($r=0\cdot66$, $p<0\cdot0005$) for patients in all three groups (Fig. 1).

We used Spearman's rank correlation (one tailed) to analyse the initial haemodynamic values for individual patients in relation to survival time from presentation. Cardiac ouput was directly related to survival ($p<0\cdot0005$). The longer the survival, the lower the pulmonary arteriolar resistance ($<0\cdot005$), systemic vascular resistance ($p<0\cdot001$), and right ventricular end diastolic pressure ($p<0\cdot025$). Correlations for mean systemic, right atrial, and pulmonary artery pressures were not significant.

Repeat catheterisations were performed in three patients in group II and all four in group III. In the group II patients (Fig. 2) there was evidence of progression with a rise in total pulmonary vascular

Table 1 *Sex and age at presentation and relation to survival*

| *Age* | *Number* | % | *Sex* | | *Mean survival time (yr)* |
|---|---|---|---|---|---|
| | | | *F* | *M* | |
| 0–15 | 7 | 20 6 | 6 | 1 | 8·7 |
| 16–45 | 19 | 55 9 | 17 | 2 | 7 9 |
| >45 | 8 | 23·5 | 3 | 5 | 4 9 |
| Total | 34 | 100 | 26<br>(76%) | 8<br>(24%) | 7·3 |

Table 2 *Clinical features at time of first presentation*

| *Clinical feature* | *Group I (n = 18) (%)* | *Group II (n = 12) (%)* | *Group III (n = 4) (%)* | *p value (I vs II + III)* |
|---|---|---|---|---|
| Examination. | | | | |
| Tricuspid regurgitation | 27 7 | 0 | 50 | NS |
| Right ventricular added sound | 50 0 | 25 0 | 50 | NS |
| Overt right heart failure | 44·4 | 8·3 | 50 | NS |
| Electrocardiogram: | | | | |
| Right ventricular hypertrophy | 100 | 83·3 | 75 | NS |
| Right axis deviation | 100 | 66·6 | 100 | <0 05 |
| Right atrial strain | 94 4 | 25·0 | 50 | <0 0005 |
| Chest *x* ray: | | | | |
| Right ventricular enlargement | 100 | 66 6 | 50 | <0 01 |
| Pulmonary artery dilatation | 100 | 100 | 100 | NS |

Table 3 *Haemodynamic features (mean (1 SD)) at first cardiac catheterisation*

| | *Groups* | | | *p value* | | |
|---|---|---|---|---|---|---|
| | *I (n=18)* | *II (n=12)* | *III (n=4)* | *I vs II* | *I vs III* | *II vs III* |
| Survival time from presentation (yr) | 2·68 (1·13) | 9·67 (4·87) | 18·75 (6·40) | <0·0005 | <0·0005 | <0·0005 |
| Catheter time from presentation (yr) | 1·44 (1·20) | 4·83 (4·95) | 5·25 (7·23) | <0·005 | <0·025 | NS |
| $\overline{\text{RA}}$ (mm Hg) | 7·56 (3·55) | 8·00 (4·63) | 6·25 (4·65) | NS | NS | NS |
| RVEDP (mm Hg) | 12·29 (4·38)* | 11·00 (5·91) | 8·75 (5·68) | NS | NS | NS |
| SPAP (mm Hg) | 97·44 (19·73) | 93·33 (32·59) | 81·50 (32·22) | NS | NS | NS |
| $\overline{\text{PA}}$ (mm Hg) | 63·89 (12·31) | 60·75 (22·43) | 53·75 (13·87) | NS | NS | NS |
| $\overline{\text{PCW}}$/LVEDP (mm Hg) | 8·33 (2·89) | 6·42 (2·87) | 5·25 (2·06) | <0·05 | <0·05 | NS |
| CO (l/min) | 2·77 (0·44) | 3·56 (1·14) | 4·30 (1·91) | <0·01 | <0·005 | NS |
| PAVR (U) | 20·66 (4·84) | 16·95 (9·35) | 12·22 (4·97) | NS | <0·005 | NS |
| $\overline{\text{SA}}$ (mm Hg) | 83·67 (11·15) | 87·92 (15·10) | 79·50 (10·79) | NS | NS | NS |
| SVR (U) | 28·33 (6·50) | 24·26 (7·95) | 18·58 (5·48) | NS | <0·01 | NS |

$\overline{\text{RA}}$, mean right atrial pressure; RVEDP, right ventricular end diastolic pressure; SPAP, systolic pulmonary artery pressure; $\overline{\text{PA}}$, mean pulmonary artery pressure, $\overline{\text{PCW}}$/LVEDP, mean pulmonary capillary wedge pressure/left ventricular end diastolic pressure; CO, cardiac output; PAVR, pulmonary arteriolar vascular resistance; $\overline{\text{SA}}$, mean systemic pressure; SVR, systemic vascular resistance.
*n = 17.

resistance and pulmonary artery pressure and fall in cardiac output. In contrast, there was clear improvement in three out of the four patients in group III (Fig. 3) with a fall in total pulmonary vascular resistance and pulmonary artery pressure and rise in cardiac output.

In the fourth patient (case 2) pulmonary artery pressure and cardiac output both fell and the haemodynamic changes were accompanied by clinical deterioration and chronic right ventricular failure. She died twelve years later of salmonella infection of her chronic ascites. Postmortem histology showed only grade 1 changes on the Heath classification[24] after she had survived more than a decade in heart failure but with a near normal pulmonary artery pressure.

Heart size and electrocardiographic evidence of right ventricular hypertrophy decreased in the three patients who did well. In two of these (cases 3 and 4) symptoms first appeared during and after pregnancy. Case 4 was given a trial of prenylamine and domiciliary oxygen soon after diagnosis and continued to take prenylamine for one year. Case 1, the

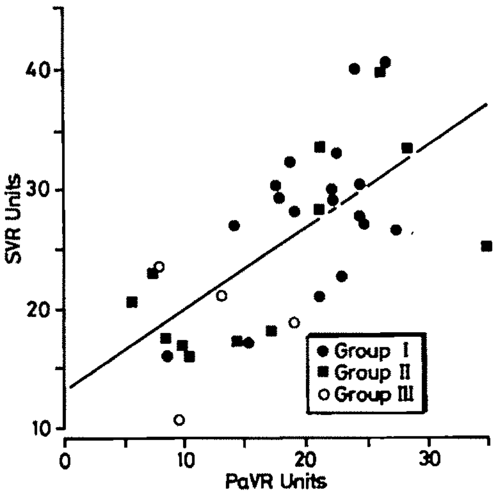

Fig. 1 *Resting haemodynamic data on first catheterisation in 34 patients with primary pulmonary hypertension. SVR, systemic vascular resistance; PaVR, pulmonary arteriolar vascular resistance. Linear regression equation:* $y = 13{\cdot}14 + 0{\cdot}687x$; $r = 0{\cdot}66$; $p = <0{\cdot}0005$.

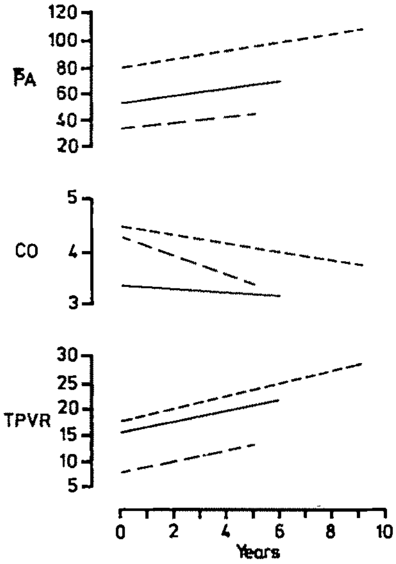

Fig. 2 *Resting haemodynamic data in the three patients of group II who had repeat cardiac catheterisation.* $\overline{\text{PA}}$*, mean pulmonary artery pressure (mm Hg); CO, cardiac output (l/mn); TPVR, total pulmonary vascular resistance (units).*

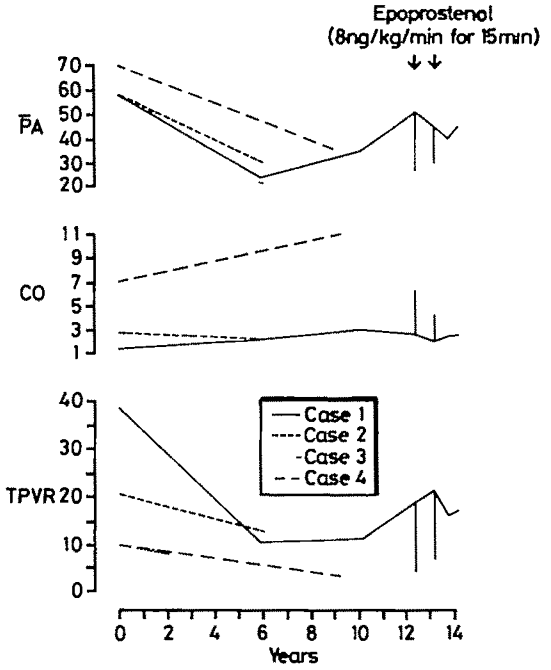

Fig. 3 *Resting haemodynamic data in patients in group III. P̄A, mean pulmonary artery pressure (mm Hg); CO, cardiac output (l/min); TPVR, total pulmonary vascular resistance (units). Data on patient 1 are indexed per* $m^2$ *because she was first studied as an adolescent.*

Table 4 *Relation of clinical and haemodynamic features to survival*

| | *Survival* | | |
|---|---|---|---|
| | *<5 yr (n=18)* | *>5 yr (n=16)* | *p value* |
| Familial disease | 1 | 1 | NS |
| Connective tissue disease | 3 | 0 | NS |
| Pregnancy | 0 | 5 | <0·02 |
| Patent foramen ovale | 0 | 4 | <0·05 |
| Right heart failure at presentation | 8 | 3 | NS |
| Right heart failure at some stage | 18 | 10 | <0·005 |

Table 5 *Mean survival after presentation and factors that may be associated with outcome*

| *Factor* | *Number* | % | *Mean survival (yr)* |
|---|---|---|---|
| Familial disease | 2 | 5·9 | 6 |
| Connective tissue disease | 3 | 8·8 | 3·4 |
| Pregnancy | 5 | 14·7 | 14·2 |
| Patent foramen ovale | 4 | 11·8 | 11·5 |
| No related factors | 20 | 58·8 | 5·5 |
| All patients | 34 | 100 | 7·3 |

subject of a previous report,[16] deteriorated again after a pregnancy and spontaneous abortion (Fig. 3) but she has subsequently improved, though pulmonary artery pressure remains raised. Epoprostenol (prostacyclin), a powerful vasodilator, was infused at a dose of 8 ng/kg/min for 15 minutes, and on both occasions produced short term haemodynamic improvement. She is almost symptom free, as are the other two. None of group III had a patent foramen ovale.

In five cases lung histology was traced. Two showed Heath grade 3 changes[24]; one each in group I and II. A further two, both in group I, had grade 5 changes. In the fifth patient from group III, case 2 described above, there was evidence of a fall in pulmonary artery pressure for at least eight years before death and only grade 1 changes. Three patients had associated connective tissue disease (systemic sclerosis, systemic lupus erythematosus, and rheumatoid arthritis). In two of these histological assessment was available; neither had evidence of pulmonary vasculitis.

Tables 4 and 5 list associated factors that might influence survival. Two patients had a relative with proven primary pulmonary hypertension. The three patients with connective tissue disease lived for <5 years after presentation. The outcome was significantly better when pulmonary hypertension first appeared during pregnancy ($p<0·02$). All five had symptoms towards the end of pregnancy. None went into right heart failure. Two had had one previous uneventful pregnancy. In one patient (case 1) there had been an improvement until her spontaneous abortion. Although right heart failure at presentation was not predictive of a poor outcome, an episode of documented right heart failure at some stage during follow up was associated with poor prognosis ($p<0·01$). Again, case 1 was an exception. The presence of a patent foramen ovale improved prognosis ($p<0·05$).

## Discussion

The diagnosis of primary pulmonary hypertension is reached by exclusion. Five patients in this series did not have pulmonary angiograms. Most perfusion lung scans were normal. In primary pulmonary hypertension minor perfusion defects accompanied by normal ventilation on lung scan are sometimes seen,[18 19] without histological evidence of pulmonary emboli[25] whereas chronic thromboembolic pulmonary hypertension always causes major defects. We made every attempt to include only those patients who fulfilled current criteria for pulmonary hypertension of unknown cause.[8 25]

The diagnosis can only be established with certainty by examination of a representative lung biopsy specimen of adequate size[2 26 27]; this was achieved in five patients. During the period of this study there were four patients with pulmonary veno-occlusive disease; in two the diagnosis was confirmed by lung biopsy and in all it was subsequently confirmed at necropsy. Six patients had thromboembolic pulmonary hypertension. These 10 patients were excluded from the series.

All but two of the patients were first catheterised when aged >17 years. Onset in childhood is less common.[2 28] The sex distribution, with a predominance of females after the menarche is similar to that reported in other series.[2 3 5] The reasons for this are unknown[8] and this observation is as true of familial as of non-familial primary pulmonary hypertension.[29] The finding that a greater proportion of male patients had late onset disease is supported by a previous study.[7] Again, the reason for this is unknown.

Age at presentation to hospital rather than onset of symptoms was taken as our reference point, because onset is inevitably poorly defined in such a slowly progressive condition. There was no relation between age at presentation and mean survival, and this accords with previous work.[3] The frequency of symptoms was similar to those already reported.[3 8 12] Breathlessness is usually the first and almost universal complaint.[3 8 12] No patients in our series gave a history consistent with digital vasospasm but not all can be assumed to have been directly questioned about this. The onset of symptoms occurred slightly earlier in those surviving for >5 years. Survival in adults is regarded as being independent of the age of onset.[2 3]

Outcome was poor when clinical right heart failure was evident at presentation to hospital or developed subsequently. The association of right heart failure with mortality is as true of primary pulmonary hypertension[5 6 30] as it is of pulmonary hypertension associated with ingestion of aminorex[6] and thromboembolic disease.[31] Non-invasive measures of right ventricular load and right ventricular size and mass from the electrocardiogram and *x* ray were no more useful for predicting outcome than were clinical features in those with right heart failure. The pulmonary artery size was unhelpful and is known not to correlate with pulmonary artery pressure in this condition.[32]

The haemodynamic features in the three groups reflected the nature of the disease course and outcome (Table 3). The patients of group II were catheterised later in their course than those of group I (Table 3) and their catheter findings indicated more advanced disease. Nevertheless, pulmonary arteriolar resistance was less in patients surviving >5 years from presentation. Pulmonary arteriolar resistance was inversely related to cardiac output, in keeping with the effects of increased afterload on right ventricular function,[33 34] and pulmonary artery pressure was not significantly different in the three groups. This has been the usual finding because most patients are not catheterised before an advanced stage of their disease is reached.[8] In the few with less advanced disease, pulmonary artery pressure increased with time (Fig. 2). Mean right atrial pressure and right ventricular filling pressure, indices of right ventricular preload, were lower in those who improved than in those who died within five years. There was no difference between groups I and II, perhaps because of the diuretics used to treat patients with overt heart failure. Furthermore, haemodynamic measurements are known to be labile in this condition, and presumably reflect spontaneous variation in pulmonary vascular tone and right ventricular function.[35] In the group as a whole, increased right ventricular afterload, a low cardiac output, and raised right ventricular filling pressure were of most significance in predicting a poor outcome. As expected the level of pulmonary artery pressure was unrelated to outcome.

Little attention has been paid to the systemic circulation in this condition. The lower the cardiac output the higher the systemic resistance. No important pathological changes are seen in the resistance vessels of the systemic circulation in primary pulmonary hypertension. Selective vasodilatation of the pulmonary circulation is accompanied by a fall in systemic resistance as cardiac output rises.[8 33] It follows that the systemic changes are secondary to those in the lung vascular bed. The compensatory changes in systemic resistance with alteration in cardiac output serve to maintain a constant blood pressure, as in other physiological settings. Not surprisingly, systemic and pulmonary arteriolar resistance were closely and directly related (Fig. 1).

On average, left ventricular filling pressure was highest in patients in group I and lowest in group III. The greater the restriction in venous return to the left heart, the lower the expected left atrial pressure. The fact that the opposite was seen in this study may reflect the decreased compliance of the left ventricle in chronic pulmonary hypertension,[36] or, more likely, the difficulty in obtaining an accurate wedged pressure. Decreased compliance may be secondary to the influence of the hypertrophied right ventricle on left ventricular shape and on the mobility of the ventricular septum.[20 36] It is unlikely that there is important systolic dysfunction[36] since left ventricular filling pressure is not raised and a rise in cardiac output follows the use of a pulmonary vasodilator without a change in filling pressure.[33,37]

All three patients who had repeat catheterisation after deterioration showed the expected rise in pulmonary arteriolar resistance and fall in cardiac output.[8,38] Pulmonary artery pressure rose only slightly (Fig. 2). The opposite pattern of haemodynamic changes was seen in the three patients in whom symptoms remitted (Fig. 3). The improvement appears to have been independent of initial severity and presentation in right heart failure. The prenylamine and oxygen may have influenced disease progression in case 4. Epoprostenol (prostacyclin) was used in one patient (case 1) as part of a separate study.[39] This naturally occurring agent can reverse vasoconstriction and prevent platelet deposition and release within the lung bed.[40–42] One report of long term improvement with continuous epoprostenol infusion,[43] does not, however, establish that it is more useful than other pulmonary vasodilators, which can also produce long term benefit.[44–46] Spontaneous regression of pulmonary hypertension in three of our patients suggests that vasolidators, by lowering pulmonary vascular resistance before lung damage is too advanced and pulmonary reactivity is lost,[47,48] may reduce pulmonary artery pressure, thereby preventing further deterioration.[49] Similarly, regression may have occurred in the patient (case 2) in whom pulmonary artery pressure fell as right heart failure occurred. It is more usual for histological changes to advance as lung blood flow falls since this reduction is normally a consequence of right heart failure as pulmonary resistance continues to rise.[12] Only Heath grade 1 changes were seen at necropsy. Assuming the lung histology was representative,[26] the two patients with grade 3 changes also had potentially reversible disease.[50] As we have seen, spontaneous regression occurs, although up to now there have been only four reported cases,[6,8,17] one of which is in this series.[16] It seems that pulmonary vascular changes may not always be irreversible even in patients who have clinically advanced disease. Improvement in the clinical state or a fall in pulmonary artery pressure, by whatever means, cannot be equated with regression of pathological changes. This is seen in the fatal case recently reported of a child who died from severe primary pulmonary hypertension but who at necropsy had only relatively mild histological changes in the lung vessels.[51] In pulmonary hypertension secondary to anorectics, regression is more frequent,[4,6] and the prognosis is better.[6] This is presumably because the onset is recent and the cause is known and removable and this may also apply to patients who present with the disease in pregnancy.

Factors linked to survival were sought. The presence of another member of the family with primary pulmonary hypertension did not predict outcome. There were only two such patients, however, and a systematic search of the families of other probands might have showed more. Familial primary pulmonary hypertension is generally considered to be inherited as an autosomal dominant trait with varying penetrance.[2,29] Although all three patients with connective tissue disease survived less than five years, the outcome in these patients was not significantly worse. Death from right heart failure secondary to pulmonary hypertension occurred a considerable time after the appearance of the initial symptoms.

Connective tissue disease is closely linked with Raynaud's phenomenon, and both are associated with primary pulmonary hypertension.[2,11,12] There are several ways by which these entities are interconnected. Firstly, all are more frequent in females. Secondly, in Raynaud's disease and Raynaud's phenomenon the lungs and the extremities are affected. Cold stimulation can cause a reduction in the size of the pulmonary capillary bed in patients with Raynaud's disease and early Raynaud's phenomenon.[52] The likely mechanism of this change is precapillary vasoconstriction,[52] and implies a generalised mechanism for progressive vascular damage. In scleroderma there is a histological basis for this in that similar changes develop in both digital and pulmonary arteries.[53] It is not known if patients with Raynaud's disease ever develop primary pulmonary hypertension. Lastly, the lupus anticoagulant, which is associated with an increased risk of spontaneous thrombosis,[54] is found in some systemic lupus patients with apparently non-embolic pulmonary hypertension.[55]

Because all patients received anticoagulants their role in primary pulmonary hypertension could not be assessed. Recurring small pulmonary thromboemboli, undetected until histology is obtained, are thought by some to contribute to the deterioration seen in patients with primary pulmonary hypertension.[27] This is far from certain.[2] Patients might benefit from the prevention of both thrombosis in situ and secondary emboli. Outcome may be improved by the use of anticoagulants.[27] Antiplatelet and fibrinolytic agents were not used in our series. Disturbance of fibrinolytic[56,57] and platelet function[58–61] can occur in pulmonary hypertension although the changes may be secondary rather than primary. Nevertheless, such agents could be of benefit, and particularly so in pulmonary hypertension associated with oral contraception[14,62] and pregnancy.[63]

Pregnancy at diagnosis seemed to be a favourable prognostic factor. None of the five patients died during a total of eight pregnancies but three of these took place before the onset of symptoms and there was only one further pregnancy after diagnosis. The reported mortality of pregnancy in women with primary pulmonary hypertension is near 50%[15,64] with a subsequent mean survival of less than five years.[15] Our cases presented in late pregnancy or after delivery, and reflected the increased load put on the right ventricle at this time. One of the five patients had a patent foramen ovale. She presented during pregnancy but miscarried. Radiography in childhood showed that she had had pulmonary hypertension at least from the age of 12 years. A patent foramen ovale, by permitting right ventricular unloading, may have accounted for her survival.[65] The favourable outcome for the pregnant group was in part because of spontaneous improvement in two (cases 3 and 4). Prolonged survival after presentation (Table 5) might reflect the onset of symptoms earlier in the disease because of the stress of pregnancy or because of some element of reversibility after pregnancy, if this event had accelerated a vasoconstrictive process.

A patent foramen ovale was associated with longer survival. This is in keeping with the better life expectancy of patients with pulmonary hypertension associated with atrial septal defect than with primary pulmonary hypertension.[65] Such a shunt, by operating at times of increased demand, permits adequate left ventricular filling and prevents sudden death.[9,10] In the absence of a shunt, exercise and systemic vasodilatation may be associated with hypotension and syncope.[66] The main mechanism for this appears to be inability of the right ventricle to increase its output, perhaps aided by ischaemia secondary to lowered coronary perfusion and increased resistance to right ventricular subendocardial flow.[67–69] Sudden death frequently occurs in primary pulmonary hypertension and usually in the setting of underlying chronic heart failure.[8] Surgical creation of an acute shunt by atrial septostomy in a patient with primary pulmonary hypertension was, however, unsuccessful due to the sudden demand put on the left ventricle in the immediate postoperative period.[70]

In conclusion, primary pulmonary hypertension is a heterogeneous disease that often has a better outcome than expected. Prognosis is largely determined by the integrity of the right ventricle. A patent foramen ovale may ameliorate the effect of increased afterload on right ventricular function. Patients in whom the onset of the disease is associated with pregnancy survived longest. Spontaneous regression was more frequent than previously reported and this suggests that early diagnosis and pharmacological treatment of primary pulmonary hypertension may be successful in some patients if the disease is detected early. Methods for such detection and a better understanding of the pathophysiology of the disease are needed.

We thank Mr M Casebow for statistical assistance.

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*Br Heart J* 1986; 55: 459–61

# Percutaneous transluminal balloon angioplasty in restenosis of coarctation of the aorta

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SUMMARY Percutaneous transluminal balloon angioplasty was performed in five children with coarctation restenosis. After angioplasty the pressure gradient had decreased considerably in four patients. In all patients aortography showed an increase in the diameter of the lumen at the site of the restenosis. All patients were normotensive the day after angioplasty. There were no complications during or after the procedure.

Surgical repair of aortic coarctation has become a safe and successful procedure.[1] Despite the use of newer techniques such as patch angioplasty, and the subclavian flap procedure, however, there is still a considerable incidence of coarctation restenosis, especially when operation has been performed in infancy.[2 3] Reoperation in these patients is associated with a higher morbidity and mortality and with less adequate relief than primary coarctation repair.[4] Recently, percutaneous transluminal angioplasty has been shown to be a promising treatment for coarctation restenosis.[5–7]

We present the results of percutaneous transluminal angioplasty for coarctation restenosis in five children who had had different types of primary surgical repair.

## Patients and methods

Five patients, aged 1·5 to 14·3 years (mean 8·2 years) underwent cardiac catheterisation and subsequent percutaneous transluminal angioplasty because of systemic hypertension due to coarctation restenosis. Three patients had had primary coarctation repair by means of resection and end to end anastomosis, one by a subclavian artery flap procedure, and one by end to side anastomosis of the left subclavian artery on the descending aorta because of the local anatomical situation. The ages at primary repair ranged from 3 days to 6·2 years (mean 1·7 years). In four children angioplasty was performed under general anaesthesia.

The pressure gradients across the restenosis were measured and the cardiac indices were calculated from dye dilution curves before and 20 minutes after angioplasty. Percutaneous transluminal angioplasty was performed with Meditech balloon dilatation catheters. The diameters of the balloons that were used ranged from 8 mm to 18 mm and the size was selected according to the coarctation diameter (measured at aortography) multiplied by 2·5. The balloon diameter never exceeded 1·2 × the diameter of the descending aorta. The dilatation catheter was positioned at the site of the restenosis over a guide wire the tip of which was advanced into the ascending aorta. Under continuous fluoroscopy the balloon was inflated to pressures of 4 atm with a 3:1 dilution of contrast medium.

This procedure was carried out three times. Each inflation lasted for about 10 seconds. After angioplasty the balloon catheter was withdrawn, and the tip of the guide wire was kept in the ascending aorta. A multipurpose catheter was then carefully introduced over the guide wire to the ascending aorta. This catheter was used for repeated aortography, pressure measurements, and dye sampling for calculation of the cardiac indices.

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Accepted for publication 14 January 1986

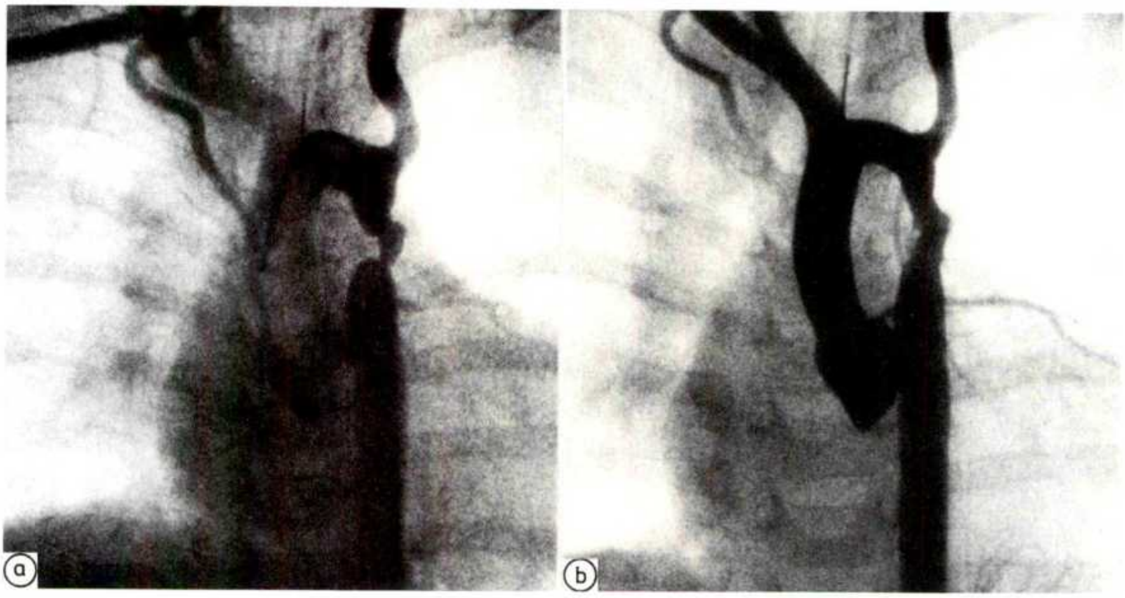

Fig. 1 *Aortography before (a) and after (b) percutaneous transluminal balloon angioplasty in a patient in whom a subclavian flap operation had been performed. There is a considerable increase of the diameter of the restenosis after angioplasty.*

## Results

There were no complications during or after the procedure. In three patients the balloon ruptured, but this caused no noticeable reaction.

Before angioplasty the systolic pressure gradients across the coarctation restenosis ranged from 15 to 49 mm Hg (mean 27 mm Hg.) The cardiac indices ranged from 2·4 to 3·6 l/min/m$^2$ (mean 3·1 l/min/m$^2$). At aortography four patients had a circumscribed restenosis and one had a tubular narrowing. This patient had the smallest pressure gradient.

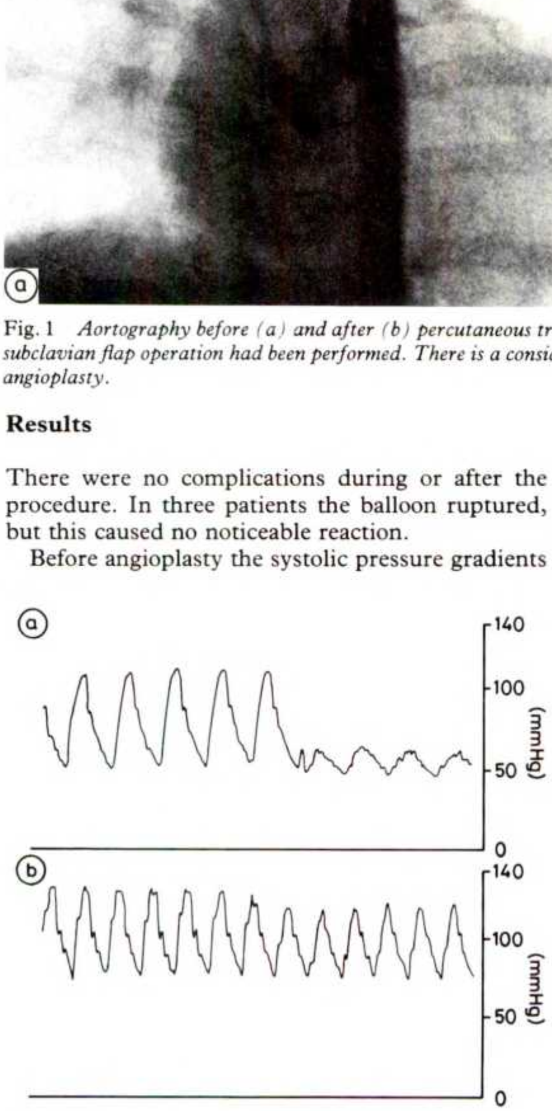

Fig. 2 *Pressure withdrawal curve from the ascending to the descending aorta in the same patient before (a) and after (b) percutaneous transluminal balloon angioplasty.*

After percutaneous transluminal balloon angioplasty the systolic pressure gradients had decreased in four patients (range 5 to 21 mm Hg, mean 12·2 mm Hg). At aortography there was an increase of the lumen diameters of the restenosis in all patients that ranged from 25% to 89% (mean 70%) of the diameters before angioplasty. In the patient with tubular narrowing angioplasty did not reduce the pressure gradient. Yet the angiographic appearance of this segment indicated an increase in diameter. The cardiac index after angioplasty ranged from 4·0 to 4·5 l/min/m$^2$ (mean 4·2 l/min /m$^2$).

All patients were normotensive the day after angioplasty.

## Discussion

Our data indicate that percutaneous transluminal angioplasty for coarctation restenosis improved all five patients. In all patients there was a substantial increase of the coarctation diameter; in four this was associated with a considerable decrease in the pressure gradient. According to the criteria of Lock *et al* (that is the combination of a 30% or larger increase in the diameter at the restenosis and a greater than 50% fall in the gradient after dilatation) percutaneous transluminal angioplasty was successful in these four patients, and the clinical response was good. The fall in the gradient is an important determinant of the blood flow across the coarctation. All patients had a pronounced increase of the cardiac index after angioplasty, and this masks the result to a certain extent. The effect probably explains the apparently poor result in the patient with the tubular stenosis. This patient, however, had had upper body hypertension for a long time and was normotensive the day after angioplasty.

Percutaneous transluminal angioplasty has been accepted as an alternative to operation. It is a safe procedure for pulmonary valve stenosis with results that are comparable to surgery.[8-10] The success rate in pulmonary branch stenosis is only 50% but angioplasty should be considered in patients in whom operation is not feasible because of the localisation and multiplicity of lesions.[11-12]

Valvar aortic stenosis in some cases has been reported to be amenable to angioplasty; however, no definite conclusions can yet be drawn about its possible advantages over surgical intervention.[9] Although the short term benefits of angioplasty for primary aortic coarctation are known, there is concern about the long term follow up.[5 7 13] The efficacy of percutaneous transluminal angioplasty depends upon disruption of intima and part of the media of the vessel.[14] This may result in areas of medial thinning. The formation of associated aneurysms has not been described but these might develop later in life.[15] In the case of coarctation restenosis the presence of scar tissue should reduce or even prevent the occurrence of this complication. There has been a report of one death after percutaneous transluminal angioplasty for coarctation restenosis; however, this was not related to disruption of the vessel.[6] Although follow up studies are needed to evaluate the long term results of percutaneous transluminal angioplasty for coarctation restenosis, the procedure seems to offer a relative safe and effective alternative to reoperation that may be used after all types of primary surgical repair.

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*Br Heart J* 1986; 55: 462–8

# Ambulatory blood pressure and assessment of pacemaker function

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SUMMARY Ten patients in sinus rhythm with ventricular demand (VVI) pacemakers implanted for the sick sinus syndrome underwent 24 hour ambulatory blood pressure and electrocardiographic recording by a modified version of the Oxford system. Five patients had symptoms of dizziness or presyncope at the time of study and five were symptom free. The onset of pacing was associated with a fall in arterial blood pressure in both groups which was larger in the patients with symptoms, and in these patients the blood pressure recovery consequent on baroreflex activation was delayed by up to fifteen beats. In three of the patients with symptoms the original pacemaker was replaced by an atrioventricular pacing (DVI) device. This abolished symptoms and the initial fall and delayed recovery of blood pressure. Thus it appears that the development of symptoms of hypotension after the onset of ventricular pacing is determined by the rate of the baroreflex response. These symptoms and the haemodynamic consequences may be alleviated by dual chamber pacing.

A patient's electrocardiographic response to an implanted pacemaker is usually assessed in the outpatient clinic where the rate, pulse width, and other variables of the stimulus artefact are analysed at periodic intervals. Ambulatory electrocardiography has become an accepted additional method for the assessment of pacemaker function.[1 2] Recent developments in Holter monitoring have facilitated recognition of the pacing stimulus artefact by detecting it separately and recording a marker pulse alongside the electrocardiogram on a two channel recorder.[2 3] Such ambulatory recordings have proved valuable in various situations, such as detecting failure to capture, failure to sense, and myopotential inhibition.

Some patients, however, have symptoms despite pacemaker function which is electrocardiographically normal. It has been suggested that these can be alleviated in patients with carotid sinus hypersensitivity by the implantation of an atrioventricular sequential (DVI) pacemaker.[4] Alicandri *et al* investigated three patients with symptoms of near syncope after ventricular pacing, and demonstrated hypotension after the onset of pacing.[5] Although these studies provided much useful information they were limited to the laboratory setting.

We have used the Oxford system for recording direct arterial pressure in ambulant subjects to study a group of patients in sinus rhythm paced for sick sinus syndrome with ventricular demand (VVI) pacemakers. Several patients had symptoms during our study; in three of these the original pacemaker was later replaced by a DVI device and a second study was performed.

We examined whether there was any systematic difference in the effects of pacing on blood pressure between those patients who complained of symptoms and those who did not. We particularly wished to observe the time course of any changes in blood pressure that might accompany the onset of pacing, and the compensatory response of the circulatory system. Ambulatory monitoring affords an ideal opportunity to study these effects quantitatively because many episodes containing the onset of pacing may be obtained from each patient.

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Accepted for publication 11 February 1986

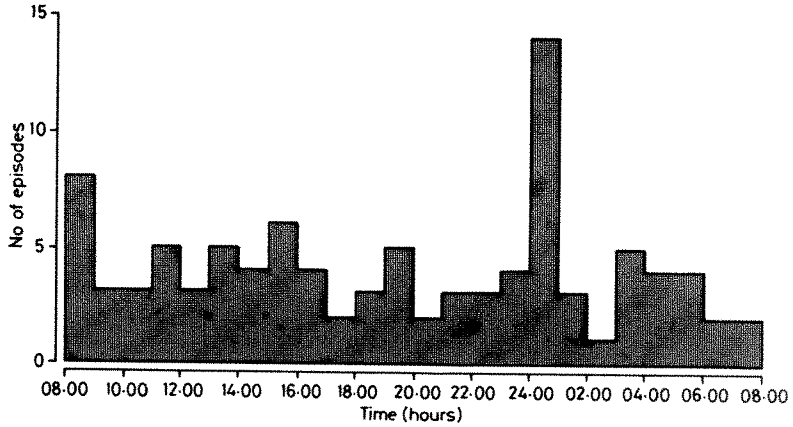

Fig. 1 *Distribution of the selected episodes of the onset of pacing throughout 24 hours.*

## Patients and methods

Thirteen patients were recruited for this study and eighteen 24 hour recordings were performed. Data of adequate technical quality for analysis were obtained from ten patients in a total of thirteen 24 hour recordings. The patients gave their informed consent in writing and the study was approved by the hospital ethical committee. We studied only patients in whom sick sinus syndrome had been diagnosed before pacemaker implantation. None was taking any cardioactive drugs at the time of the study and none was in atrial fibrillation. In all of them a 24 hour ambulatory electrocardiographic recording was performed before the study to detect any evidence of electrical pacemaker malfunction.

Ambulatory recordings of direct arterial blood pressure and electrocardiogram were obtained with a modified Oxford Medical Systems Medilog MKI Recorder. The technique for ambulatory recording of direct arterial blood pressure has been described.[6] After insertion of a brachial artery cannula, patients were allowed to be fully ambulant; they returned to the hospital every 12 hours for equipment checks and were asked to keep a diary of any symptoms that they experienced during the recording period. Four patients had symptoms of light headedness or presyncope during their first 24 hour recording. In three of these patients the original pacemaker was replaced by a DVI device and a second period of 24 hour recording was performed.

### RECORDING EQUIPMENT

The standard Oxford Medilog electrocardiogram recorder does not register pacemaker signals accurately because of its limited high frequency capability. To distinguish reliably between paced and unpaced beats a pacing spike detector (Reynolds

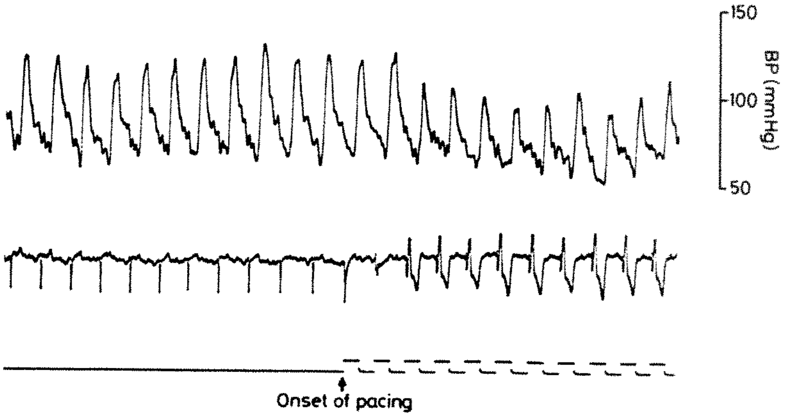

Fig. 2 *Direct arterial blood pressure measurement, electrocardiogram, and pacing spike detector during the onset of VVI pacing in a patient without symptoms.*

Medical Electronics) was installed in the recorder. This module sensed the pacing activity in a surface electrocardiogram from an extra pair of electrodes that were positioned to maximise the spike amplitude while minimising other electrocardiogram components. The sensing electrode was usually placed over the V1 position and the reference electrode over the implanted pacemaker. The pacing spike detector module converted each spike into a pulse of 250 ms duration which was recorded on tape track 2 alongside the normal electrocardiogram on track 1.[3] An alternative version of this technique in which the same electrode pair was used for both electrocardiogram and pacemaker recording has been described elsewhere.[7]

### TAPE ANALYSIS

The tapes were replayed at 25 times the recorded speed into a hybrid computing system[8] that was slightly modified for pacemaker spike detection. The continuous blood pressure and pulse interval were extracted for each cardiac cycle. Track 2 of the tape was simultaneously scanned for paced beats. Each tape was first replayed in full to produce a trend chart of every paced beat in the 24 hours. From the trend chart an observer (HP) selected all episodes containing at least 20 beats of sinus rhythm followed by at least 20 beats of continuous pacing. At this stage she did not know which patients had symptoms. The episodes selected were then processed by the computer. A total of 100 episodes were analysed. Fig. 1 shows the distribution of these episodes throughout each 24 hours.

For each episode in which sinus rhythm changed to continuous pacing the beat by beat blood pressure and pulse interval values were printed out together with a marker indicating whether beats were paced or not. The signal timing was such that for each paced beat detected the corresponding printout showed the systolic pressure which occurred immediately after the pacing spike, the diastolic pressure which followed this systolic value, and the interval between this diastolic minimum and the preceding diastolic minimum. The same timing convention was used for unpaced beats. For these the R wave was used as the fiducial marker. For each episode, the printed results were checked by reference to a photographic chart writeout of the blood pressure, electrocardiogram, and pacing spike detector pulses (Fig. 2).

### STATISTICAL METHODS

The 72 episodes initially selected during VVI pacing were divided into two groups: those from the patients with symptoms (40 episodes) and those from the symptom free patients (32 episodes). The length of the episodes varied from 40 to 80 cardiac cycles; beats were numbered negatively and positively about the onset of pacing (defined as beat zero).

The data were first analysed in terms of absolute values of blood pressure before, at the onset of pacing and 5, 10, and 15 beats after pacing. The individual blood pressure responses, and the mean changes in blood pressure during this period were then considered. Although this method of analysis provided some insight into the behaviour of blood pressure in response to pacing the wide individual variation in responses produced a smoothing effect in which the time course of the response was not apparent.

We therefore performed a further statistical analysis of each of the 72 episodes in which the beat by beat blood pressure was searched for significant rises or falls by regressing blood pressure on beat number within a window eleven points in length that could be moved along the entire length of the episode. At each position of the window the best fit was determined; a significant fall in blood pressure (blood pressure increase followed by decrease) was considered to be present if the regression yielded a negative quadratic component with a t statistic greater than 2 (or equivalently an F statistic greater than 4). Similarly a significant rise in blood pressure (blood pressure decrease followed by increase) was said to have occurred if the regression yielded a significant positive quadratic component. If either type of response was found, the position of the midpoint of the window was noted. The window was then moved one beat to the right and the next regression was performed. By this means, the position of any significant peaks or troughs in the systolic data sequence could be determined relative to the onset of pacing, irrespective of the actual pressure values or heart rates. The results from all 72 episodes were then grouped for patients with and without symptoms. The rises and falls in blood pressure were plotted separately and for each of these four subgroups the observed and expected numbers of significant responses were compared by a $\chi^2$ test. When we calculated the expected distribution of responses we took into account the differing lengths of the raw data episodes. Therefore, for each position relative to the onset of pacing, the expected number of positive responses was evaluated as the total positive responses at all positions multiplied by the proportion of episodes containing valid data at the current position. The expected distribution of negative responses was similarly calculated.

We also compared ($\chi^2$ test) the number of significant rises and falls in blood pressure in the patients with symptoms and those without. In three

Table *Clinical data in 10 patients*

| *Patient No* | *Age* | *Sex* | *Pacemaker type* | *Time since implant* | *Symptoms* |
|---|---|---|---|---|---|
| 1* | 60 | M | CPI Microlith | 2 yr | Presyncope |
| 2 (a)* | 67 | F | CPI Microlith | 3 yr | Presyncope |
| (b) | | | DVI Medtronic | 2 mnth | Nil |
| 3 | 69 | M | CPI Microlith | 2 mnth | Nil |
| 4 | 71 | M | Precilith | 3 mnth | Nil |
| 5 (a)* | 70 | M | CPI Microlith | 1 yr | Presyncope |
| (b) | | | DVI Cyberlith | 2 mnth | Nil |
| 6 | 72 | M | CPI Microlith | 3 yr | Nil |
| 7 | 55 | M | CPI Microlith | 4 mnth | Nil |
| 8 (a)* | 68 | M | CPI Microlith | 6 mnth | Presyncope |
| (b) | | | DVI Microlith | 2 mnth | Nil |
| 9 | 72 | M | Unilith | 5 yr | Nil |
| 10* | 58 | M | CPI Microlith | 6 mnth | Presyncope |

Patients undergoing re-study (a and b).
*Patients with symptoms

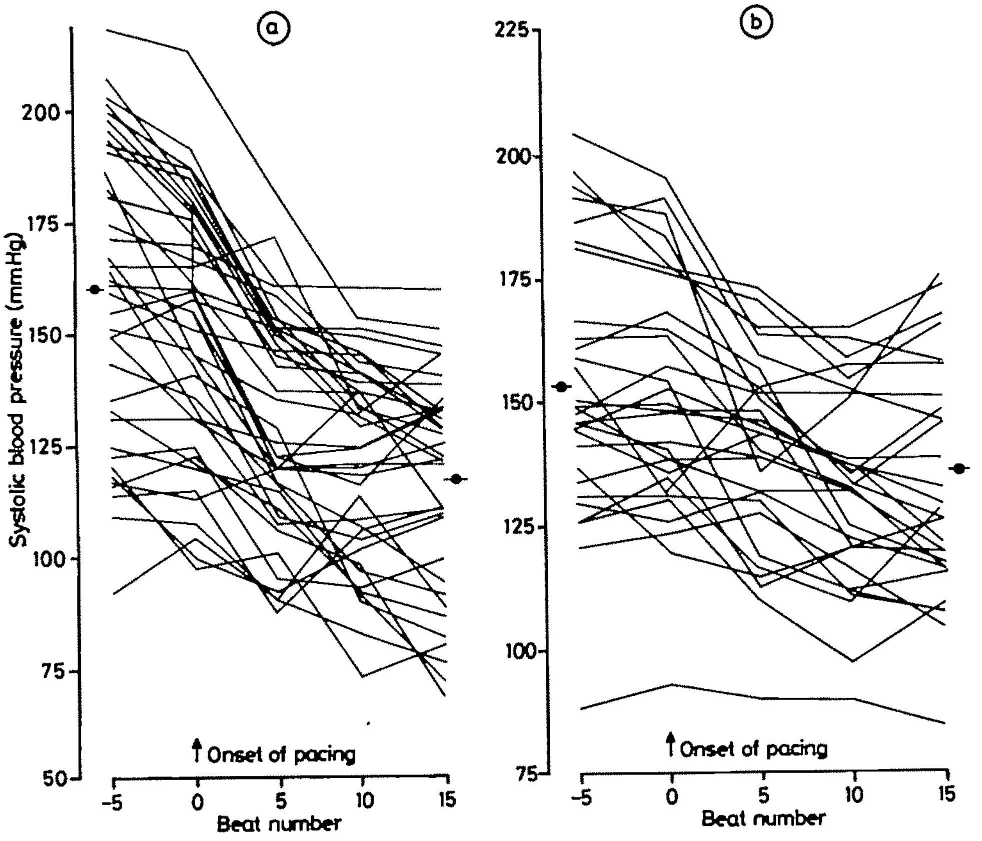

Fig. 3 *Individual changes in blood pressure during each of the selected episodes in patients with symptoms (a) and in those without (b).*

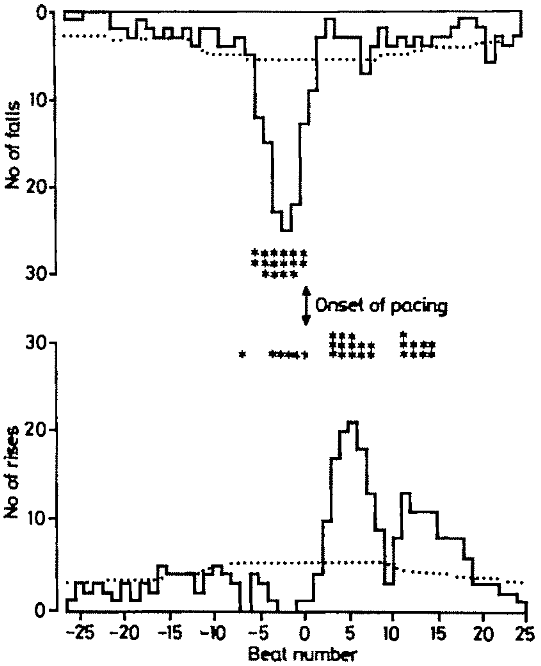

Fig. 4 *Effects of VVI pacing on systolic blood pressure in five patients with symptoms. The number of episodes expected (see text) is indicated by the broken line.* $*p < 0.05$; $**p < 0.01$; $***p < 0.001$.

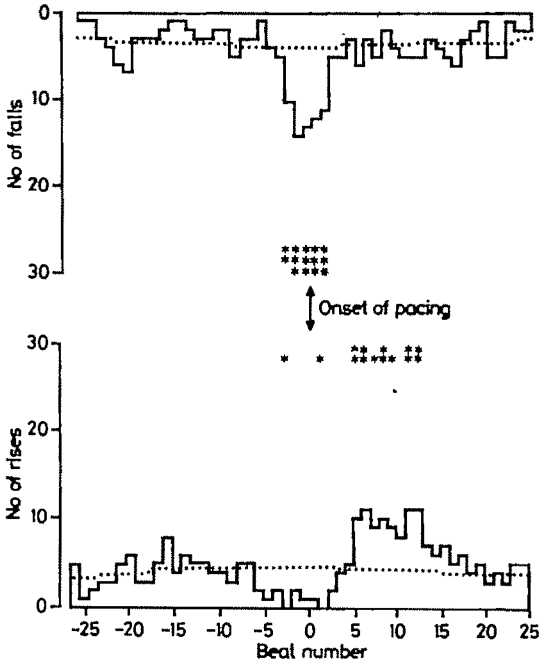

Fig. 5 *Effects of VVI pacing on systolic blood pressure in five symptom free patients. The number of episodes expected is indicated by the broken line.* $*p < 0.05$; $**p < 0.01$; $***p < 0.001$.

patients results before (27 episodes) and after (28 episodes) replacement of their VVI pacemaker with a DVI device were also compared.

## Results

Five recordings were excluded from the analysis, two because of pump artefact, one because of only very short episodes of sinus rhythm, and two because the pacemaker detector failed to trigger. Figure 1 shows the distribution of the selected episodes throughout the 24 hours; there was an increase at 24.00 hours, presumably associated with retiring to bed.

The Table shows the clinical data for the ten patients. Of the two patients who had symptoms at the time of the first study and who were not restudied, one had episodes of hypoglycaemia which were thought to be responsible for his symptoms and one declined a change of pacemaker. The individual changes in blood pressure during each of the selected episodes were plotted for patients with symptoms and for those without (Fig. 3). The mean fall in blood pressure was 40 (21) mm Hg in those with symptoms and 18 (15) mm Hg in those without symptoms ($p < 0.001$). Figure 4 shows the effect of pacing on systolic blood pressure in patients with symptoms, and Fig. 5 results in patients without symptoms. Pacing induced a fall in blood pressure in both groups. This was followed by a compensatory rise after five beats. Patients with symptoms, however, had a considerable number of delayed compensatory responses, unlike those without symptoms. A direct statistical comparison showed that there were significantly fewer rises and falls in blood pressure in the symptom free patients and significantly more in those with symptoms ($p < 0.001$).

Figure 6 shows the response of systolic blood pressure during VVI pacing in three of the patients with symptoms. The pattern of response (a fall followed by two different rates of recovery) was maintained in this group. After the original pacemaker was replaced by a DVI device both the fall in blood pressure at the onset of pacing and the subsequent compensatory rise were abolished (Fig. 6), as were the patients' symptoms. In both groups, with and without symptoms, a similar, although less pronounced, response was seen in diastolic blood pressure.

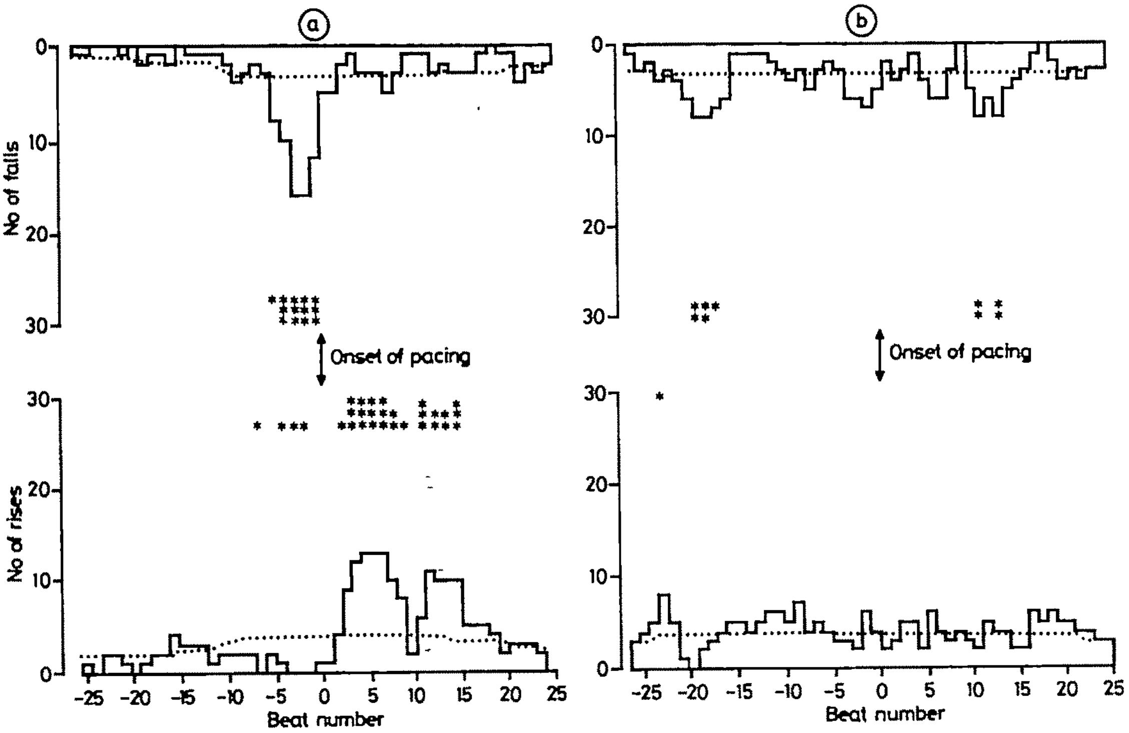

Fig. 6 *(a) Effects of VVI pacing on systolic blood pressure in three patients with symptoms. (b) Effect in same patients after substitution of a DVI pacemaker The number of episodes expected is indicated by the broken line.* *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

## Discussion

The pacemaker syndrome or pacemaker effect, with the development of hypotension after the onset of ventricular pacing, is well recognised; however, its incidence and importance is disputed. Cohen *et al* recently suggested that atrial transport was of clinical importance in 19 (7·3%) of 260 consecutive patients undergoing implantation of a permanent pacemaker.[9] Their patients developed symptoms ranging from dizziness and syncope to congestive heart failure and shock. Alicandri *et al* have suggested that the level of arterial blood pressure during VVI pacing is determined by two opposing reflexes, the baroreflex which attempts to compensate for a reduction in cardiac output, and an atrial distension reflex that leads to a reduction in peripheral vascular resistance.[5]

Using the technique of ambulatory monitoring and selecting only patients with underlying sinus rhythm, we obtained a large number of episodes of a change from sinus to paced rhythm for further study. Analysis of the time course of the blood pressure response confirmed that the onset of ventricular pacing produced a fall in blood pressure in all patients. In patients with symptoms, however, two types of recovery pattern were seen with recovery delayed by fifteen beats (±13 seconds) during some episodes. These findings suggest that as well as the fall in blood pressure it is the duration of hypotension induced by an impaired baroreflex response which is important in the development of symptoms.

Two of the three patients who complained of symptoms experienced dizzy spells during their first 24 hour recording. The patients' diaries were not considered sufficiently accurate to relate symptoms to specific haemodynamic events. Separate analysis of the blood pressure responses during VVI pacing in the three patients with symptoms in whom the original pacemaker was later replaced showed an identical pattern of recovery. These findings imply that both types of recovery (immediate or delayed) may occur in an individual patient, depending on the circumstances at the time of onset of pacing. The benefit of implanting an atrial electrode and DVI generator in these three patients was clearly demonstrated. Their symptoms were alleviated, and analysis of the blood pressure response during pacing showed that the initial fall in blood pressure, and hence the need for baroreflex activation, was abolished.

It is possible that the time course of the recovery in blood pressure is in part related to the rate at which atrioventricular desynchronisation occurs, and the duration of hypotension may be influenced by the rate at which atrioventricular synchrony is restored. The heart rates before the onset of pacing were similar in the two patient groups. Unfortunately the quality of electrocardiographic recording in most patients was inadequate for further analysis of atrioventricular synchronisation. Although it would be difficult to perform invasive haemodynamic studies in all patients complaining of presyncope after pacemaker implantations, the results of this study suggest that an impaired baroreflex response to a fall in cardiac output is of importance in determining the development of symptoms. This group of patients seems to benefit from the substitution of a dual chamber pacing device.

We thank Professor C E Rossiter for advice and guidance on the statistical analysis procedures, and Dr M C Petch for his helpful comments during the preparation of this paper.

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*Br Heart J* 1986; 55: 469–74

# Familial spontaneous complete heart block in hypertrophic cardiomyopathy

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SUMMARY Two siblings with hypertrophic cardiomyopathy developed spontaneous complete heart block requiring permanent pacemaker implantation at similar ages (29 and 33 years). The clinical, morphological, and haemodynamic expressions of hypertrophic cardiomyopathy differed considerably in these two patients. The sister had severe functional limitation due to dyspnoea, pronounced and diffuse left ventricular hypertrophy (maximum ventricular septal thickness of 41 mm), and left ventricular outflow obstruction (peak subaortic gradient of 75 mm Hg under basal conditions). In contrast the brother was symptom free, had only modest left ventricular hypertrophy which was confined to the anterior ventricular septum (maximal thickness of 16 mm), and had no echocardiographic evidence of subaortic obstruction. These dissimilar findings in siblings with hypertrophic cardiomyopathy suggest that the predisposition to develop complete heart block was probably genetically transmitted, although it was unrelated to the phenotypic and clinical expression of the disease.

Hypertrophic cardiomyopathy is a primary myocardial disease, usually genetically transmitted as an autosomal dominant trait.[1-3] This disease is characterised by great heterogeneity in the patterns of left ventricular hypertrophy[4] that are present even among closely related patients.[5] Complete heart block is rare in patients with hypertrophic cardiomyopathy, and its aetiology has not been defined. Sporadic examples, however, have been reported at all ages including those in a neonate in whom the abnormality was congenital[6] and in several young adults.[7-12] Complete heart block that was apparently unrelated to acquired cardiac disease has also been reported in older adults[13-16] and in elderly patients[17-21] with hypertrophic cardiomyopathy.

Recently, we have evaluated a sister and brother with hypertrophic cardiomyopathy who both developed complete heart block as young adults. We believe that such an occurrence is particularly unusual and represents an opportunity to assess and discuss the potential aetiology of complete heart block in this disease. Hence, the present report describes and compares the clinical and morphological features identified in a sister and brother with hypertrophic cardiomyopathy and complete heart block.

## Case reports

*Sister*—The sister had experienced exertional dyspnoea and fatigue attributed to hypertrophic cardiomyopathy for seven years and also had a history of mild systemic hypertension (165/100 mm Hg while off medications and normal blood pressure on alpha methyldopa (1 g per day) and propranolol (30 mg per day)). At initial evaluation at the National Institutes of Health, a grade 3/6 systolic ejection murmur which increased during the Valsalva manoeuvre was present at rest; the electrocardiogram showed normal sinus rhythm (65 beats per minute) and left bundle branch block pattern. At cardiac catheterisation under basal conditions, pull-back recordings from the left ventricular apex to the ascending aorta showed systolic pressures of 240 mm Hg in the distal left ventricular cavity and 165 mm Hg in the outflow tract. A 75 mm Hg peak to peak systolic pressure gradient was apparently localised to the

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Accepted for publication 10 December 1985

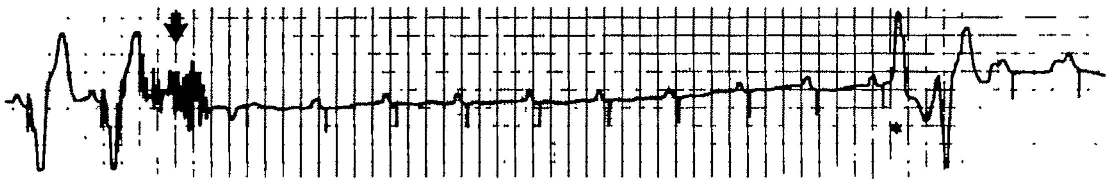

Fig. 1 *Electrocardiogram confirming persistence of complete heart block (18 months after its onset) in the sister. At the left the tracing shows normal pacemaker function (atrial sensing and ventricular pacing with 100% capture). Subsequently (arrow) the pacemaker output was programmed to subthreshold levels; this resulted in pacemaker spikes which failed to capture the ventricles and unmasked P waves which do not conduct to the ventricles. A seven second period of ventricular asystole ensued before the appearance of a ventricular escape beat (asterisk).*

mid-ventricular cavity level distal to the tips of the mitral valve leaflets (and not associated with systolic anterior motion of the mitral valve on angiogram or M mode echocardiogram); during the Valsalva manoeuvre the pressure gradient increased to 120 mm Hg. Left ventricular end diastolic pressure was 26 mm Hg.

Subsequently (at 33 years of age) the patient experienced a prolonged episode of lightheadedness and was found to have a heart rate of 20 beats per minute. Electrocardiogram showed complete heart block with sinus P waves which failed to conduct to the ventricles and a slow idioventricular escape rhythm that was different from her previously identified left bundle branch block pattern. These electrocardiographic findings are consistent with an infranodal conduction block; however, in the absence of intracardiac His potential recordings a higher level of block cannot be excluded. Serum electrolyte, calcium, and creatine kinase concentrations were normal.

Permanent pacing was started with a Cordis 233 F pacemaker. At follow up one and a half years later the electrocardiogram showed ventricular pacing with 100% capture; complete heart block was confirmed by programming the output of the pacemaker to subthreshold levels. This uncovered the sinus P waves that failed to conduct to the ventricles and resulted in a seven second period of ventricular asystole (Fig. 1).

*Brother*—The brother had not been evaluated for cardiovascular disease before the onset of complete heart block. He was symptom free until the age of 29 years when he fainted four times within a two week period. After the fourth episode of syncope he was found to have pronounced bradycardia (30 beats per minute). The electrocardiogram showed complete heart block. As in his sister's case an infranodal level of block was indicated by the failure of sinus P waves to conduct to the ventricles and the presence of a slow idioventricular escape mechanism, though a more proximal level of block cannot be excluded. Serum electrolyte, calcium, and creatine kinase concentrations were normal.

Permanent pacing was started with an Intermedics 253-04 pacemaker. At follow up two and a half years later the electrocardiogram showed ventricular pacing with 100% capture; complete heart block was confirmed by programming the rate of the pacemaker to 30 beats per minute. This uncovered sinus P waves which failed to conduct to the ventricles.

On physical examination a grade 1/6 systolic ejection murmur was heard along the left sternal border which did not change appreciably with the Valsalva manoeuvre; blood pressure was 150/90 mm Hg. The

Table *Echocardiographic findings in siblings with hypertrophic cardiomyopathy and complete heart block*

| *Variable* | *Sister* | *Brother* |
|---|---|---|
| Ventricular septal thickness (mm) | 41 (8–12)* | 16 (8–11) |
| Posterior free wall thickness (mm) | 8 (8–11) | 9 (8–11) |
| Septal to free wall ratio | 3·9 (<1·3) | 1·8 (<1·3) |
| % Systolic thickening of septum | 0 (>30%) | 25 (>30%) |
| LV end diastolic dimension (mm) | 42 (42–53) | 50 (41–52) |
| LV end systolic dimension (mm) | 26 (25–36) | 30 (24–35) |
| % Fractional shortening | 38 (28–44%) | 40 (28–44%) |
| RV end diastolic dimension (mm) | 18 (9–26) | 21 (9–26) |
| Left atrial dimension (mm) | 48 (30–44) | 41 (30–43) |

*Normal values or range are shown in parentheses.[25–27]
LV, left ventricle; RV, right ventricle.

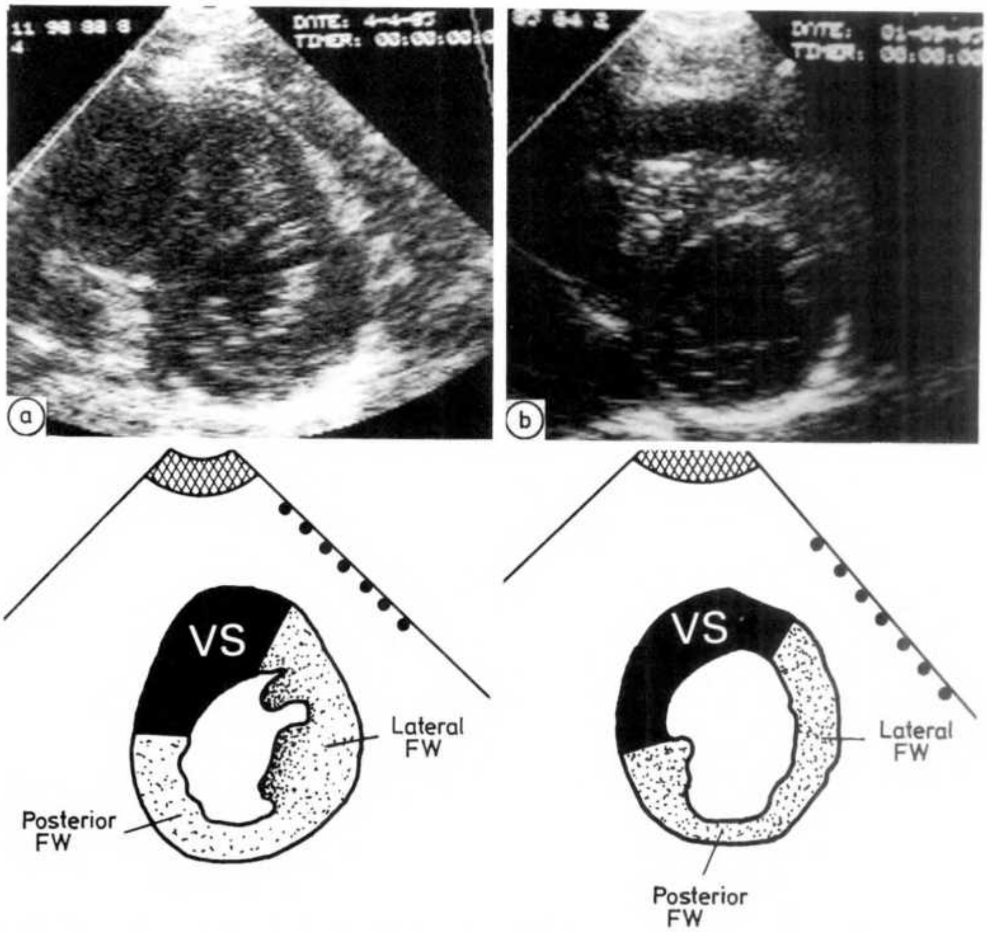

Fig. 2 *Stop frames of short axis echocardiograms obtained during diastole showing contrasting morphological features in the sister and brother. Each echocardiogram is accompanied by a schematic illustration (below). (a) Pronounced ventricular septal thickening and substantial hypertrophy in the contiguous anterolateral free wall in the sister. (b) Mild anterior ventricular septal thickening in the brother; other areas of the left ventricular wall are of normal thickness. FW, free wall; VS, ventricular septum. Calibration dots are 10 mm apart.*

absence of both an important heart murmur and of systolic anterior motion of the mitral valve on echocardiographic studies suggests the absence of a subaortic pressure gradient under basal conditions. The patient did not undergo cardiac catheterisation.

*Echocardiographic findings in siblings*
The M mode echocardiographic findings in the two siblings are compared in the Table. In each patient the left ventricle was not dilated and the pattern of left ventricular hypertrophy was asymmetric (ventricular septal to posterior free wall ratios were 3·9 in the sister and 1·8 in the brother). Cross sectional echocardiography showed the magnitude and distribution of hypertrophy to be markedly different in the siblings (Fig. 2). The sister had pronounced diffuse hypertrophy affecting the entire ventricular septum (maximum thickness of anterior septum 41 mm) as well as the contiguous portion of the anterolateral left ventricular free wall (thickness of 22 mm). In contrast the brother showed only mild wall thickening (16 mm) (Fig. 3) which was confined to the anterior ventricular septum; the posterior septum and the left ventricular free wall appeared normal in thickness. Neither patient demonstrated systolic anterior motion of the mitral valve (Fig. 3).

*Echocardiographic analysis of other family members*
Genetic transmission of hypertrophic cardiomyopathy was demonstrated in relatives of the two

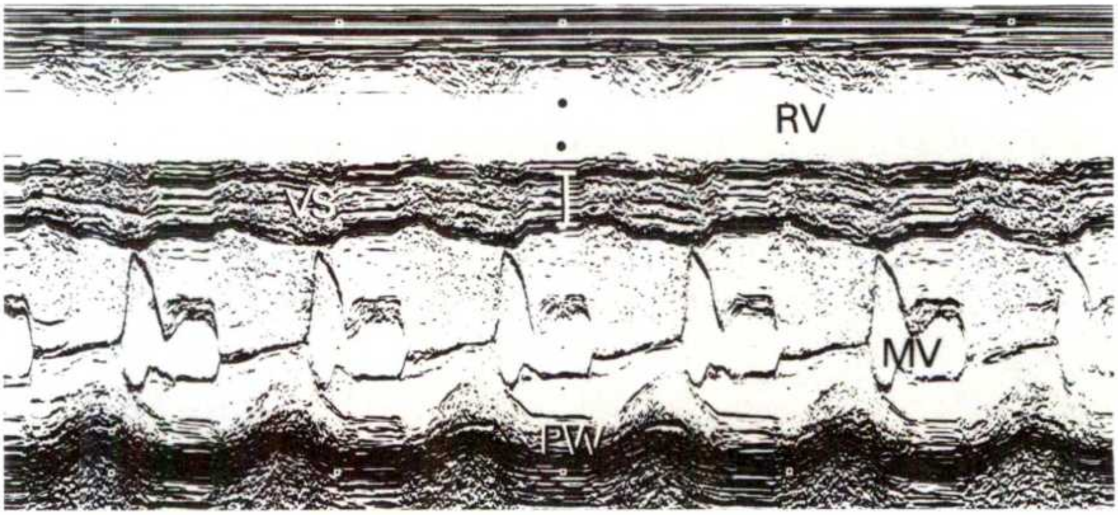

Fig. 3 *M mode echocardiogram at the mitral valve level obtained in the brother. The ventricular septum is slightly thickened whereas the posterior wall is of normal thickness, resulting in a septal to free wall ratio of 1·8. There is no systolic anterior motion of the mitral valve. MV, mitral valve; PW, posterior wall; RV, right ventricle; VS, ventricular septum. Calibration dots are 10 mm apart.*

siblings (Fig. 4). Their mother (who is symptom free) showed an increased ventricular septal thickness of 20 mm, left ventricular posterior free wall thickness of 10 mm, and a septal to free wall thickness ratio of 2·0; the left ventricle was non-dilated and the end diastolic transverse dimension was 42 mm. Systolic anterior motion of the mitral valve was absent. She had no evidence of systemic hypertension or other cardiac diseases that could produce left ventricular hypertrophy.

In addition the siblings' maternal uncle and maternal grandmother died suddenly at 28 and 38 years of age respectively. While we assume that these two relatives had hypertrophic cardiomyopathy, this diagnosis could not be confirmed in either individual because neither clinical evaluation during life nor necropsy examination of the heart were performed.

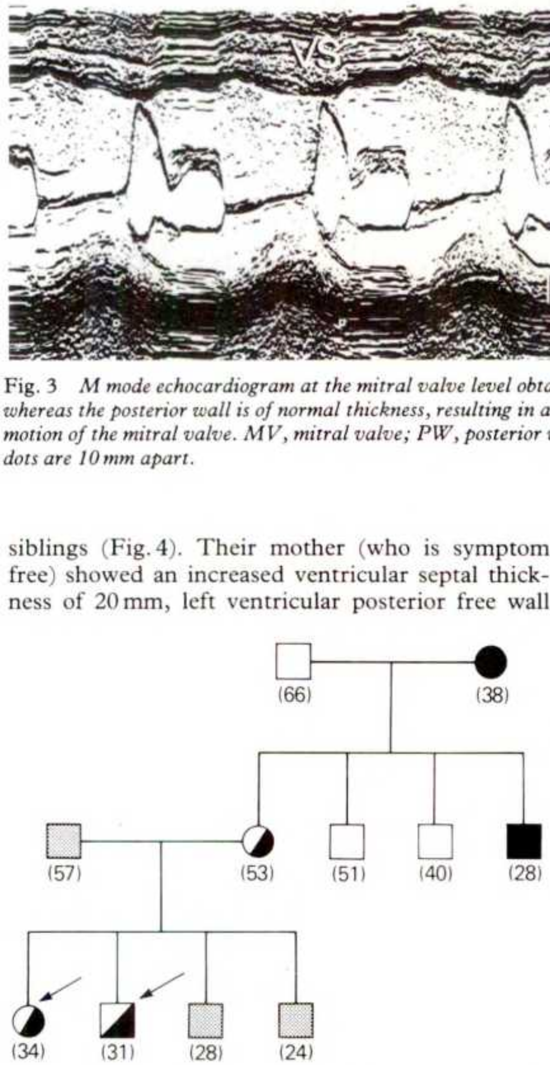

Fig. 4 *Family pedigree for the two siblings (arrows) with hypertrophic cardiomyopathy and complete heart block. Patient's ages (in years) at most recent follow up or at death are shown in parentheses. Solid symbols, sudden death presumed to be due to hypertrophic cardiomyopathy; half-filled symbols, alive with hypertrophic cardiomyopathy identified by echocardiography; stippled, alive with no evidence of hypertrophic cardiomyopathy on echocardiographic studies; clear symbols, individuals not studied with echocardiography; squares, males; circles, females.*

## Discussion

This report describes the unusual occurrence of spontaneous complete heart block in two youthful siblings with hypertrophic cardiomyopathy. Onset of heart block was accompanied in each patient by syncope or lightheadedness and pronounced bradycardia necessitating the implantation of a permanent pacemaker. Neither patient had evidence of other cardiovascular abnormalities or metabolic alterations that could have been responsible for the development of complete heart block. While both siblings had a history of mild systemic hypertension, it is highly unlikely that this condition could have produced complete heart block in such youthful individuals. Propranolol, which was taken by the sister, is not known to prolong the HV interval or produce infranodal heart block at usual therapeutic dosages.[14] The mother of these two siblings with hypertrophic cardiomyopathy and complete heart block had no evidence of clinically overt connective tissue disease.[22]

The precise mechanism by which complete heart block occurred in our patients.has not been defined. Previous histopathological analyses of the conduction system in two patients with hypertrophic cardiomyopathy and advanced conduction system disease (one with HV prolongation and split His potentials and the other with complete heart block) identified alterations of potential pathophysiological importance, including interstitial fibrosis or myocardial necrosis and abnormal small intramural coronary arteries with thickened walls and luminal narrowing.[12 23]

Whereas both our patients had hypertrophy affecting the basal septum in the region of the conduction system, the magnitude of septal thickening did not appear to be an important aetiological factor in producing complete heart block. The sister had pronounced and diffuse left ventricular hypertrophy with substantial ventricular septal thickening (in excess of 40 mm); however, the brother showed only mild localised anterior septal thickening (of about 15 mm). Indeed, these patients illustrate the heterogeneity and dissimilarity of patterns of left ventricular hypertrophy that are characteristic of first degree relatives with hypertrophic cardiomyopathy.[5]

Obstruction of the left ventricular outflow tract does not appear to be necessary for the spontaneous development of complete heart block in hypertrophic cardiomyopathy. The sister had a pronounced intraventricular pressure gradient at rest which appeared to be confined to the mid-cavity region of the left ventricle and was not associated with mitral systolic anterior motion,[24] while the brother (who did not undergo cardiac catheterisation) had no echocardiographic evidence of basal subaortic obstruction.

The sister had had complete left bundle branch block pattern on electrocardiogram for at least six years before the occurrence of complete heart block. It is tempting to speculate[16] that her left bundle branch block was indicative of pre-existing disease of the conduction system and was a forerunner of the subsequent complete heart block.

The dissimilar clinical, morphological, and haemodynamic expressions of hypertrophic cardiomyopathy in our two siblings suggest that the predisposition to develop complete heart block was genetically transmitted but was largely unrelated to the phenotypic and clinical expression of the disease.

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# Abnormalities of the mitral valve in congenitally corrected transposition (discordant atrioventricular and ventriculoarterial connections)

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SUMMARY Abnormalities of the mitral valve were found in 16 (55%) of 29 necropsy specimens of hearts with congenitally corrected transposition of the great arteries (discordant atrioventricular and ventriculoarterial connections). These abnormalities were most commonly of cusp number (21%) and tension apparatus (21%). Dysplasia of the valve was less common (10%), and other abnormalities identified included common valve, stenosis, and cleft valve. Some of the cases showed more than one morphological abnormality. The median age at death in those cases with mitral valve abnormalities was significantly higher than those without. More females than males had valves affected (ratio 2:1). Malformations such as ventricular septal defect and tricuspid or pulmonary valve anomalies were represented in similar proportions in cases with and without mitral anomalies.

Abnormalities of the tricuspid valve (the valve of the morphologically right ventricle),[1 2] the pulmonary valve, and the subpulmonary area[3–5] are well documented in hearts with congenitally corrected transposition. Less frequently the aortic valve may be abnormal[3 6] but as far as we are aware there has been no systematic study of or reference to abnormalities of the mitral valve in this condition. This paper documents the prevalence and nature of these abnormalities in 29 necropsy cases.

Throughout this paper the term mitral valve is used to designate the atrioventricular valve of the morphologically left ventricle.

## Patients and methods

Thirty five heart specimens with congenitally corrected transposition from the pathological collection at Killingbeck Hospital were examined for evidence of abnormality of the mitral valve. After initial inspection six hearts were discarded because of extensive tissue damage from previous dissection at operation or necropsy that precluded accurate evaluation. A detailed macroscopic examination of the atrioventricular and arterial valves was made in the remaining 29 cases. Abnormalities of the mitral valve were listed and grouped according to their major morphological characteristics.

## Results

There were 15 female and 10 male patients who were aged from 1 day to 24 years at the time of death (median 19 months). Patients with normal mitral valves (age range 1 day to 11 years, mean 1·9 years) were significantly younger at death than those in whom the mitral valve was abnormal (age range 1 day to 24 years, mean 6·5 years, SEM 2·0 years).

### MITRAL ABNORMALITIES

Abnormalities of the mitral valve were found in 16 (55%) of the 29 specimens. The Table summarises the details.

#### *Valves with multiple cusps*

A valve with more than two cusps was regarded as abnormal. In this series; one valve had three cusps, three were quadricuspid, and two had five cusps (Fig. 1). In each case the cusps were separated by

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Accepted for publication 13 January 1986

Table *Morphological features of cases with an abnormal mitral valve*

| *Case No* | *Age* | *Sex* | *Mitral abnormality* | *VSD* | *Tricuspid abnormality* | *Pulmonary outlet* | *Other abnormalities* |
|---|---|---|---|---|---|---|---|
| 1 | 22 mo | M | Multicuspid (4) | Large | Normal | Atresia | Right aortic arch |
| 2 | 24 yr | F | Tension apparatus | Small | Multicuspid (5) | Moderate stenosis | |
| 3 | ? | M | Multicuspid (3), tension apparatus, common valve | Large | Tension apparatus, common valve | Normal | TAPVC, single coronary ostium, AVSD |
| 4 | 10 wk | M | Pronounced scalloping, tension apparatus | Large | Atresia | Normal | |
| 5 | 10 mo | M | Dysplasia | None | Ebstein's | Mild stenosis* | |
| 6 | 8 yr | ? | Multicuspid (4) | Small | Stenosis | Moderate stenosis | |
| 7 | 16 yr | M | Tension apparatus | Moderate | Dysplasia | Normal | |
| 8 | 5 mo | F | Tension apparatus, cleft | Large | Tension apparatus | Atresia | Right aortic arch |
| 9 | 13 yr | F | Dysplasia | Small | Normal | Atresia | Right aortic arch, bilateral SCV |
| 10 | 14 yr | F | Multicuspid (4) | Small | Dysplasia | Moderate stenosis | |
| 11 | ? | F | Stenosis | Moderate | Ebstein's | Atresia | |
| 12 | 8 yr | M | Multicuspid (5) | None | Ebstein's | Normal | |
| 13 | 1 day | F | Pronounced scalloping, tension apparatus | None | Ebstein's | Mild stenosis* | |
| 14 | 19 mo | F | Dysplasia, common valve | Large | Dysplasia, common valve | Atresia | TAPVC, AVSD |
| 15 | 16 mo | F | Multicuspid (5) | Small | Ebstein's | Normal | |
| 16 | 11 mo | F | Pronounced scalloping | Small | Ebstein's | Moderate stenosis | |

*Pulmonary outflow tract tag or membranous septal aneurysm.
VSD, ventricular septal defect; AVSD, atrioventricular septal defect; SCV, superior caval vein; TAPVC, total anomalous pulmonary venous connection.
Figure in parentheses after multicuspid valve is number of cusps.

commissural areas defined by the presence of commissural chordae.[7] In a further three cases the posterior cusp was divided into two or more well separated sections. Shortening and dysplasia of the chordae in these cases, however, made it impossible to recognise commissural chordae. These divisions were far in excess of the scalloping of the mitral leaflets described in normal hearts.[8 9] None of the leaflets were dysplastic and, as far as it was possible to judge in fixed specimens, these abnormalities probably would not have created any haemodynamic disturbance. The valves with three cusps also had abnormalities of the tension apparatus. In nearly all of the cases in which the mitral valve had more than two cusps, the tricuspid and pulmonary valves were also abnormal; for example Ebstein's anomaly of the tricuspid valve was present in both cases in which the mitral valve had five cusps.

### *Abnormalities of tension apparatus*

Six cases (21%) had abnormalities of the tension apparatus that comprised multiple or compound papillary muscles and anomalous chordal attachment. In three cases there were multiple papillary muscles. In one this affected both anterior and posterior papillary groups, with ten papillary muscles supporting three cusps (Fig 2), while in the other two only the posterior papillary muscles were increased.

There were two cases with short dysplastic chordae. In one of these the anterior cusp of the mitral portion of a common valve was almost sessile while the posterolateral cusp had numerous papillary muscles and is included in the group mentioned above (Fig 3). The other case showed numerous short dysplastic chordae attached to a bizarre posterior papillary muscle (Fig. 4). Two cases showed parachute like malformations of the papillary muscle in that most of the chordae were attached to a single papillary muscle group. In one of these cases small tenuous chordae were attached to a delicate posterior papillary muscle. In the other, one cusp of a cleft valve had a single thick chordal attachment to one portion of a duplex papillary muscle while the remaining chordae were attached to the other portion (Fig 4).

### *Dysplasia, stenosis, common valve, or cleft*

There were three cases (10%) of valve dysplasia. Two had a rather redundant rolled edge appearance to the cusps (Fig 5) that might have resulted in incompetence of the valve. In the remaining case the dysplasia was more nodular and the valve was hypoplastic with a supravalvar ridge and appeared to be considerably stenosed (Fig. 5). Of the two cases of common atrioventricular valve one had abnormalities of tension apparatus and one case also had dysplastic leaflets. The cleft valve may also have been incompetent, but though the cleft is impressive in the fixed specimen (Fig. 4) it is impossible to be certain about the presence of regurgitation during life.

## ADDITIONAL ABNORMALITIES

In all cases the aortic valve was normal.

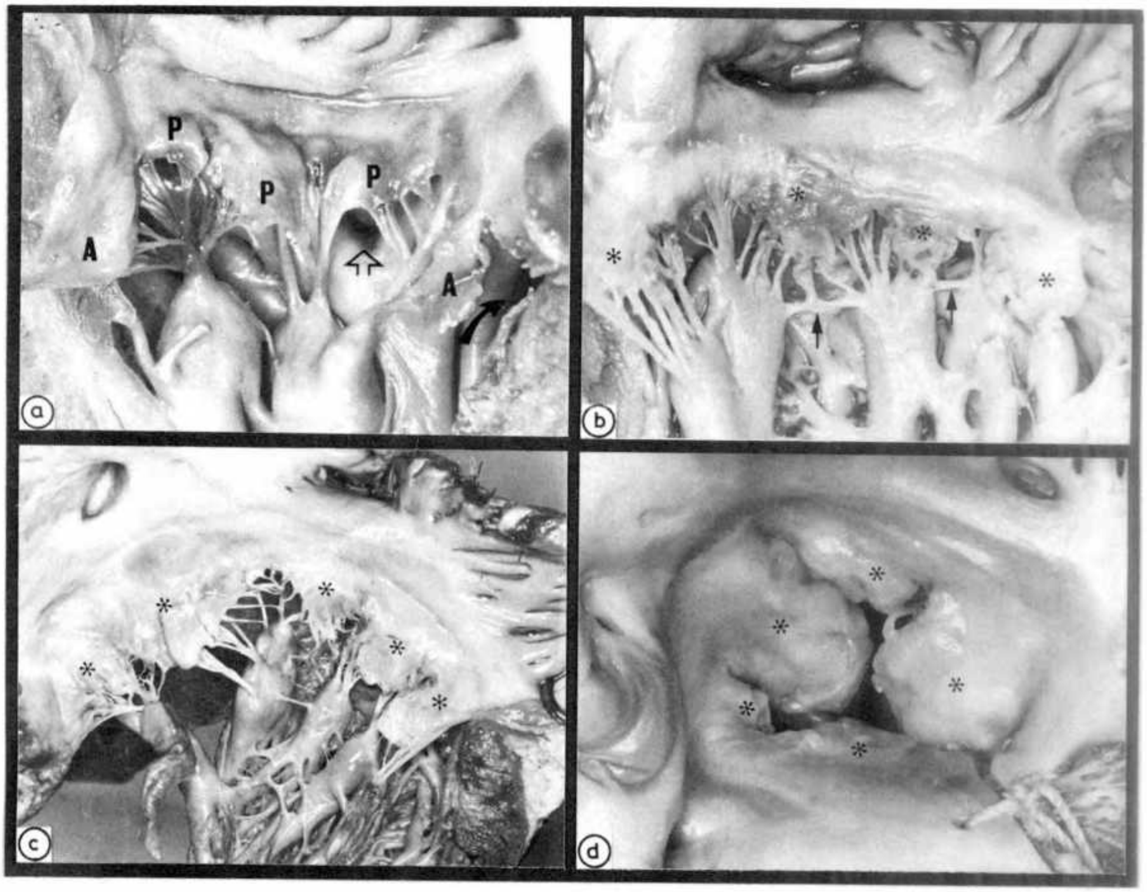

Fig. 1 *Valves with more than two cusps. (a) There are four cusps. The anterior cusp (A) has been divided. Three posterior cusps (P) are present. Closed arrow, ventricular septal defect; open arrow, pulmonary outlet (case 1). (b) Pronounced scalloping of the posterior leaflet of the mitral valve giving the appearance of four equal well formed cusps (asterisked). There is some shortening of chordae and bridging between the papillary muscles (arrowed) (case 4). (c) A valve with five cusps attached to confluent papillary muscles (case 12). (d) Atrial view of a five cusp valve in the closed position (case 15).*

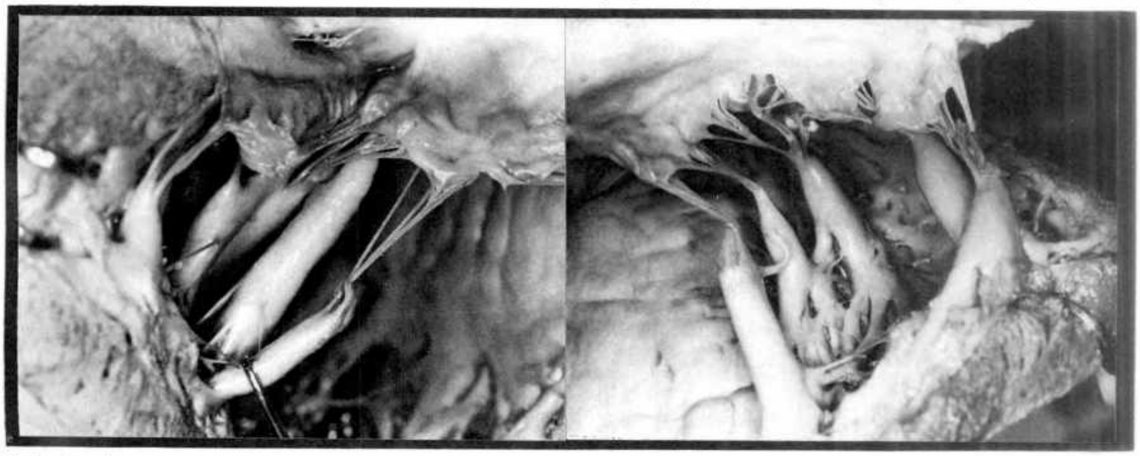

Fig. 2 *A montage view of an opened mitral valve showing ten papillary muscles in two groups of five (case 7).*

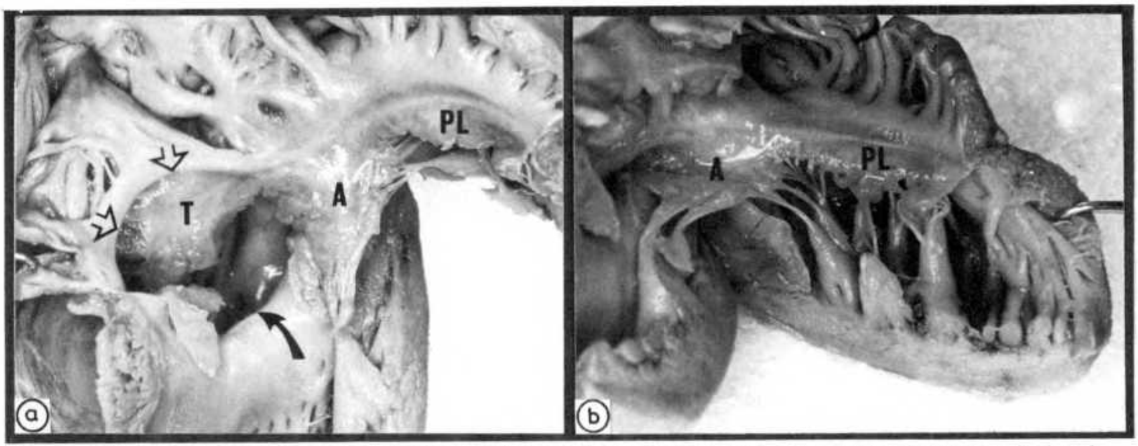

Fig. 3 *(a) The straddling atrioventricular valve associated with an atrioventricular septal defect. The specimen is viewed from behind. A, anterior mitral cusp; PL, posterolateral mitral cusp; T, tricuspid valve; closed arrow, ventricular septal defect; open arrows, margins of ostium primum defect. (b) The posterolateral cusp of the mitral valve is attached to numerous papillary muscles (case 3).*

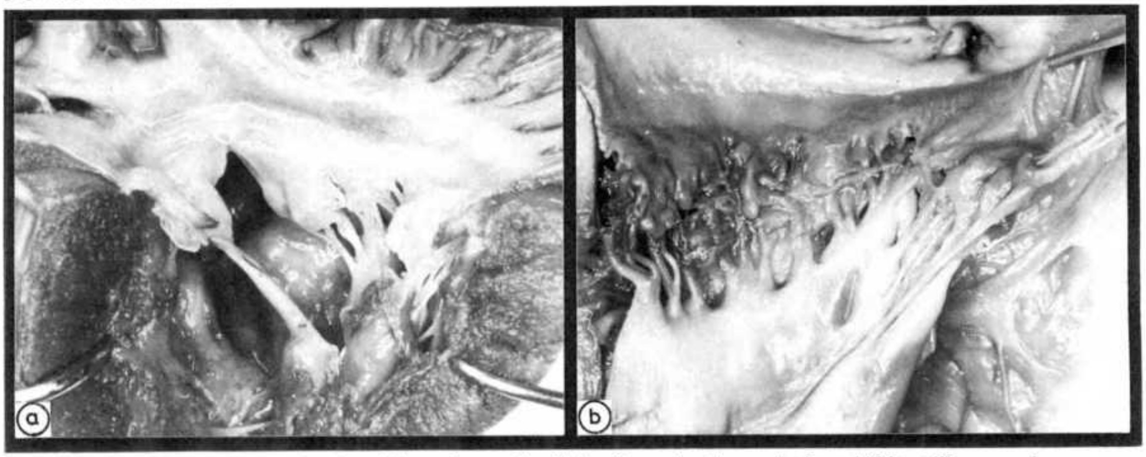

Fig. 4 *(a) A deeply cleft mitral valve with an abnormally thick solitary chorda attached to a bifid papillary muscle (case 8). (b) The posterior cusp of a mitral valve with pronounced scalloping of the posterior cusp showing the attachment of multiple shortened chordae to an atypical papillary muscle (case 13).*

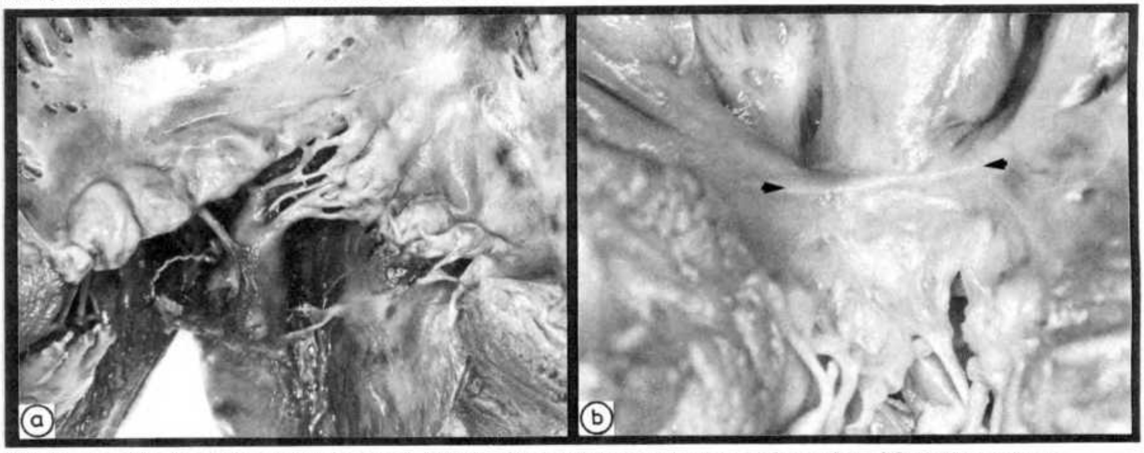

Fig. 5 *(a) The dysplastic thickened cusps of this mitral valve show some doming similar to that of floppy or mucinous degeneration. The chordae are also thickened (case 9). (b) A hypoplastic dysplastic and stenosed mitral valve with a transverse supravalvar ridge (arrowed) (case 11).*

*Tricuspid lesions*

Abnormalities of the tricuspid valve were present in 25 cases (86%). Although tricuspid valve abnormalities were represented in similar proportions in the groups with and without mitral anomalies, there were six cases of Ebstein's anomaly in the group with mitral valve anomalies against two cases in those with normal mitral valves.

*Ventricular septal defects*

Ventricular septal defects were present in 23 cases (79%) and were represented in similar proportions in the groups with and without mitral valve anomalies.

*Pulmonary valve and subpulmonary region*

Pulmonary atresia (10/29) or stenosis (9/29) were common and in addition there were five cases with subpulmonary tags or aneurysms of the membranous septum that may have caused obstruction to blood flow. Outlet abnormalities of the morphologically left ventricle were represented in similar proportions in those cases with and without mitral valve anomalies.

*Other minor abnormalities*

There were five cases with a right sided aortic arch, two cases with bilateral superior caval veins, and two cases of total anomalous pulmonary venous connection. There was one case each of single coronary ostium, left juxtaposition of the atrial appendages, and right ventricular diverticulum.

## Discussion

It is clear that in congenitally corrected transposition of the great arteries abnormalities of the mitral valve are common. Although two earlier papers refer to mitral insufficiency in this condition,[10 11] it is clear that these workers were referring to the valve of the morphologically right ventricle. It is surprising that there has been no mention of abnormalities of the mitral valve in previous detailed morphological and clinical studies of this condition.[1 2] This may be explained by the fact that the abnormalities we found, though numerous, were relatively minor and for the most part are unlikely to have produced serious haemodynamic disturbance. Attention has naturally focused on those defects which are surgically more important.

In any study of fixed specimens it is often difficult to be certain of the severity of the haemodynamic disturbance likely to result from a given anatomical lesion and in this study we felt that only in the case with stenosis of the valve would the disturbance have been important. In a further three cases, two with cusp dysplasia and one with a cleft, regurgitation might have been present during life. It is therefore unlikely that abnormalities of the mitral valve will be of surgical importance in this group of patients. Nevertheless, since our series is a small and selected group it is possible that occasionally the mitral lesion may be more important.

Although the cases with abnormal mitral valves were significantly older at the time of death than those with normal mitral valves it is clear from the nature of the mitral lesions (with the possible exception of the three cases with cusp dysplasia) that they were not acquired in postnatal life.

## Conclusion

The mitral valve anomalies we have described are minor. Whether in the long term they will become clinically important in the survivors of surgical treatment or in those rare examples of corrected transposition without additional abnormalities remains to be seen.

LMG is supported by the National Heart Research Fund.

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*Br Heart J* 1986; 55: 480–7

# Severe aortic stenosis in elderly patients

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SUMMARY Clinical and non-invasive findings were compared with catheterisation data in 91 elderly patients (mean 65 years, range 52–78) with suspected severe aortic stenosis requiring operation. Heart catheterisation showed that forty nine patients had a valve area of $\leqslant 0{\cdot}6\ \text{cm}^2$, 36 had a valve area of $0{\cdot}7$–$1{\cdot}0\ \text{cm}^2$, and six an area of $\geqslant 1{\cdot}1\ \text{cm}^2$. Coexistent aortic regurgitation was found in 85% of the cases, but severe regurgitation was found in only one patient (1%). Seventy seven per cent of patients had chest pain, 74% had dyspnoea, and 46% had exertional vertigo or syncope. Coronary angiography, which was performed in 77 patients, showed coronary artery disease in 24% of those with a history of angina pectoris and in none of those without. All patients had echodense valves; aortic valve calcification was shown by *x* ray in 76% and in all but one by cineradiography. The peak of the systolic murmur was delayed in 98% of the patients. Although a prolonged left ventricular ejection time was characteristic of severe aortic stenosis, a normal value did not exclude this diagnosis. Most patients (84%) had increased QRS amplitude on the electrocardiogram. Echocardiography showed an increased left ventricular wall thickness in 90% of the patients in whom it was possible to define the myocardial borders. There was an inadequate blood pressure increase in response to exercise in 82%. In about 25% of the patients the exercise test was at variance with the New York Heart Association classification. Findings suggesting severe aortic stenosis resembled those reported for younger age groups. When most findings point to severe aortic stenosis, the absence of a single symptom or non-invasive sign does not exclude severe aortic stenosis.

The classic symptoms of aortic stenosis—congestive heart failure, angina pectoris, and syncope—usually appear in the sixth decade or later[1 2] and without operation outcome is usually poor. Operation on elderly patients with aortic stenosis is now feasible. Studies of the diagnosis and haemodynamics of aortic stenosis have mainly been of younger patients with isolated aortic stenosis; patients with coexistent aortic regurgitation have been excluded. Usually only single non-invasive signs have been investigated, and of those studies in which a combination of non-invasive variables was used to predict the severity of aortic stenosis[3–6] only one[6] included echocardiography and none included an exercise test.

In our experience isolated aortic stenosis is rare in elderly patients. Because coexistent ischaemic heart disease is common, coronary angiography has seemed to be essential, although it was reported as being carried out in only one of the above mentioned studies.[6] Our study describes the haemodynamic, clinical, and non-invasive features in a group of elderly patients referred for catheterisation because they were believed to have aortic stenosis severe enough to merit operation.

## Patients and methods

The patients who fulfilled the above criteria were all >50 years old and numbered 94, but three of them have been excluded because their aortic valve area could not be determined at catheterisation. The remaining 91 comprised 38 women and 53 men aged 52–78 years (mean 65). Figure 1 shows the functional capacity of the 91 patients according to New York Heart Association criteria.[7] Eighteen patients

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Accepted for publication 2 December 1985

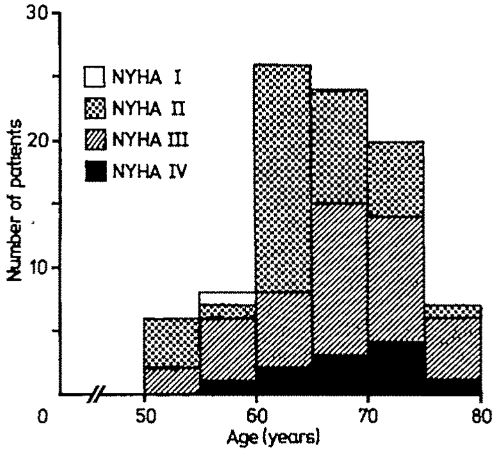

Fig. 1 *New York Heart Association classification in relation to age.*

were or had been on maintenance antihypertensive medication. Forty four patients were on digitalis, 51 on diuretics and 23 on $\beta$ blockers.

## Methods

Patient history was extracted from the medical records with particular emphasis on effort-related chest pain, dyspnoea, dizziness, and syncope. A 12 lead electrocardiogram was recorded at rest and evaluated according to the Minnesota Code.[8] An exercise test was performed with the patient seated on an electrically braked bicycle ergometer with either a stepped increase in load every sixth minute (n = 44) or with a continuous increase in workload of 10 W each minute (n = 32). Chest pain, dyspnoea, dizziness, fall in systolic blood pressure, or fatigue were used as end points. With the stepped increase in workloads, maximal work performance (Wmax 6′) was calculated according to Strandell.[9] With the continuous load increase, the workload at the interruption of the test was converted into Wmax 6′ by multiplication by a factor of 0·78.[10]

Indirect systolic blood pressure response during exercise was classified as: I a fall of $\geqslant 10$ mm Hg; II a subnormal rise, that is $\leqslant 10$ mm Hg per 30 W increase in workload; III a normal rise, that is 11 to 30 mm Hg rise per 30 W. Phonocardiography was performed from the apex in the left lateral position (A) and from the base of the heart, where the murmur was strongest (B). The maximum of the systolic ejection murmur was defined and assessed in relation to the onset of the Q wave and to the onset of the first heart sound ($S_1$). These time intervals were subsequently related to the Q-$S_2$ and $S_1$-$S_2$ times respectively. The third and fourth heart sounds were regarded as abnormal if they had increased amplitudes relative to second heart sound ($S_2$) and had a higher frequency content than normal. The carotid pulse was recorded with a system time constant of 3·2 s at a paper speed of 100 mm/s simultaneously with the electrocardiogram (lead II). Left ventricular ejection time was measured and rate corrected in three different ways.[11-13] The T time and U time were measured according to Tavel[14] and were corrected according to Bazett.[12]

All chest radiographs and cineangiograms were examined retrospectively in sequence by one experienced radiologist without knowledge of other patient data. Aortic valve calcification was independently estimated from the chest *x* rays and the cineangiography. Left ventricular angiography was performed in all patients, retrograde thoracic aortography in 87, and selective coronary angiography in 77. Aortic regurgitation was assessed semiquantitatively according to Cullhed[15] and mitral regurgitation in a similar manner.

The echocardiograms, which had been recorded at routine clinical examination, were checked and remeasured by an experienced technician who was unaware of the catheterisation results. All measurements were obtained from M mode recordings made with a 3 MHz ATL (Advanced Technology Laboratory) mechanical sector scanner with the patient recumbent in the left lateral position, according to the recommendations of the American Society of Echocardiography.[16] Left ventricular muscle mass was determined according to Bennett and Evans.[17]

All patients were catheterised, with a transseptal catheter to the left ventricle, one catheter to central aorta, and a third one to the pulmonary artery. Pressures were registered by external pressure transducers with the mid-thoracic level as a reference point. Cardiac output was determined by the Fick method. Simultaneous aortic and left ventricular pressures were recorded during the cardiac output determination and the aortic valve area was calculated by the Gorlin formula.[18]

### *Statistics*

One way analysis of variance was performed to determine the statistical significance of observed differences between the three severity groups (see below). If a significant F ratio was obtained, differences between each pair of group means were compared by Duncan's new multiple range test.[19] Linear regression coefficients were calculated by the method of least squares. Multiple regression analysis, as expected, yielded no useful relations for the evaluation of the severity of the aortic stenosis because of the uniformity of these selected patients.

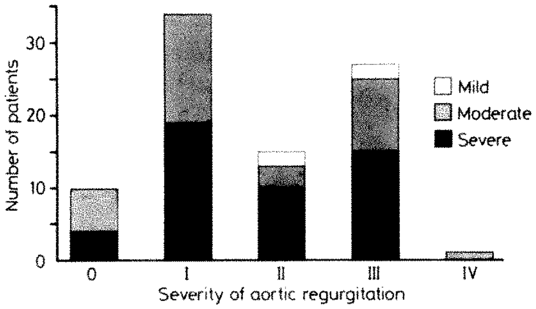

Fig. 2 *Aortic regurgitation in relation to aortic valve area. Aortic regurgitation was assessed semiquantitatively according to Cullhed,*[15] *where 0 is no regurgitation and IV is severe regurgitation. Aortography was not performed in four cases.*

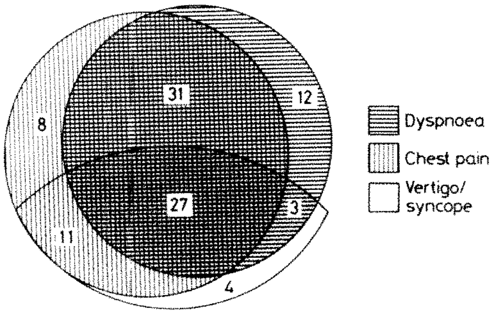

Fig. 3 *Occurrence of dyspnoea, chest pain, and dizziness/syncope. Three of the 91 patients had no symptoms and are not included in the figure.*

## Results

### *Classification*

The patients were classified according to the severity of their aortic stenosis. Forty nine patients (54%) (age 52–78, mean 67 years) were classified as having severe stenosis (aortic valve area $\leqslant 0{\cdot}6\,\mathrm{cm}^2$), 36 (39%) (age 53–76, mean 63), as having moderate stenosis (area $0{\cdot}7$–$1{\cdot}0\,\mathrm{cm}^2$), and six (7%) (age 61–71, mean 67) as having mild stenosis (area $\geqslant 1{\cdot}1\,\mathrm{cm}^2$). Seventy seven (85%) of the patients had aortic regurgitation of varying degrees, but only one patient (1%) had severe regurgitation (Fig. 2). No patient was excluded because of its presence (see Dis-

Table 1 *Haemodynamic variables*

| | *Aortic stenosis* | *No* | *Mean* | *SD* | *Range* |
|---|---|---|---|---|---|
| Aortic valve area (cm²) | Severe | 49 | 0·48 | 0·10 | 0·2–0·6 |
| | Moderate | 36 | 0·78 | 0·10 | 0·7–1·0 |
| | Mild | 6 | 1·63 | 0·66 | 1·2–2·9 |
| Peak systolic gradient (mm Hg) | Severe | 49 | 79 ** | 31 | 31–171 |
| | Moderate | 36 | ** 44 | 19 | 11–90 |
| | Mild | 6 | 18 * | 19 | 0–45 |
| Mean systolic gradient (mm Hg) | Severe | 49 | 64 * | 21 | 28–124 |
| | Moderate | 36 | ** 39 | 14 | 11–73 |
| | Mild | 6 | 18 * | 14 | 2–33 |
| Left ventricular systolic pressure (mm Hg) | Severe | 49 | 211 ** | 37 | 125–305 |
| | Moderate | 36 | ** 189 | 28 | 118–241 |
| | Mild | 6 | 164 | 34 | 110–204 |
| Left ventricular end diastolic pressure (mm Hg) | Severe | 49 | 21 | 9 | 7–40 |
| | Moderate | 36 | 18 | 8 | 7–40 |
| | Mild | 6 | 17 | 5 | 10–24 |
| Right atrial mean pressure (mm Hg) | Severe | 49 | 6 | 4 | 2–21 |
| | Moderate | 36 | 6 | 3 | 1–18 |
| | Mild | 6 | 6 | 2 | 3–8 |
| Systolic pulmonary arterial pressure (mm Hg) | Severe | 49 | 42 | 20 | 20–100 |
| | Moderate | 36 | 36 | 13 | 20–74 |
| | Mild | 6 | 37 | 6 | 27–42 |
| Arteriovenous oxygen difference (ml/l) | Severe | 49 | 57 | 11 | 39–92 |
| | Moderate | 36 | 55 | 13 | 38–94 |
| | Mild | 6 | 57 | 16 | 44–86 |
| Stroke volume (ml) | Severe | 49 | 53 * | 14 | 27–89 |
| | Moderate | 36 | ** 64 | 16 | 23–96 |
| | Mild | 6 | 70 | 24 | 30–100 |

*$p < 0{\cdot}05$, **$p < 0{\cdot}01$.

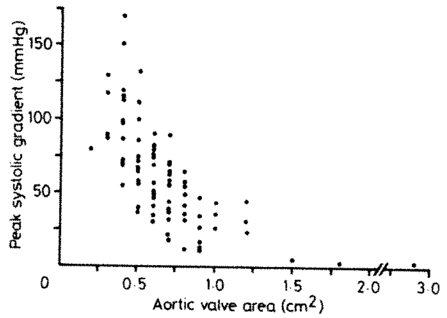

Fig. 4 *Peak systolic gradient in relation to calculated aortic valve area. No correction was made for degree of aortic regurgitation.*

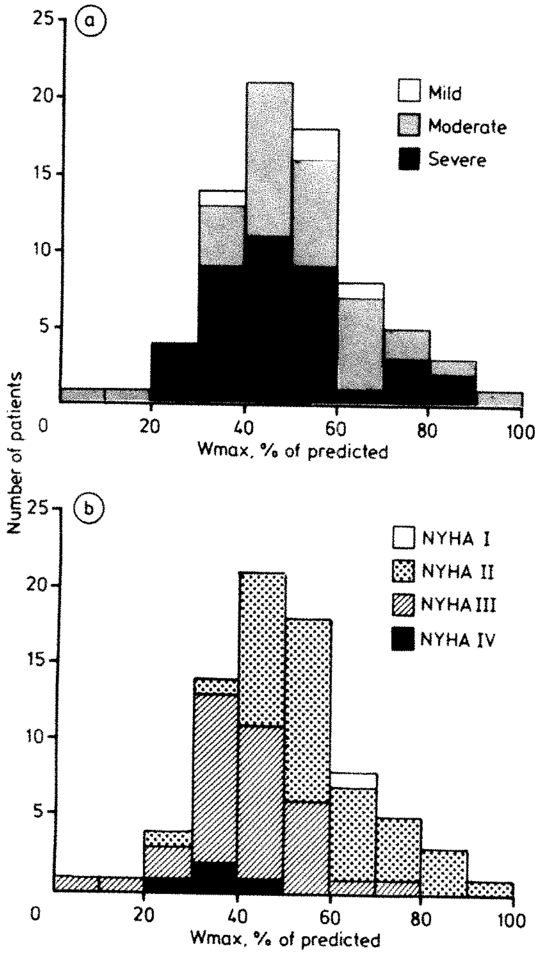

Fig. 5 *Physical work capacity at the exercise test, expressed as per cent of age and sex related reference value (Wmax%)*$^{21}$ *in relation to aortic valve area (a) and New York Heart Association classification (b).*

cussion). Twenty patients (22%) had mild mitral regurgitation and nine (10%) had moderate mitral regurgitation; these cases were equally distributed among the three aortic stenosis groups. Only two patients had severe mitral regurgitation—one in each of the groups with severe and moderate obstruction. The calculated aortic area forms the basis of the comparison with the non-invasive data.

### *Symptoms*

Seventy patients (77%) had a history of chest pain, 67 (74%) of dyspnoea, and 42 (46%) of vertigo and/or syncope, all related to exertion (Fig. 3). Twenty five patients (27%) had a combination of all these symptoms and in 24 of these 25 patients the aortic valve area was less than 1·1 cm$^2$. Three patients, however, without any of these symptoms had the same small valve area.

### *Findings at invasive investigation*

Table 1 summarises some variables that were determined invasively. As expected there is an inverse correlation between valvar area and systolic pressure gradient (Fig. 4). It is, however, notable that in individual patients with a peak systolic gradient of only 30 mm Hg the valve area was less than 0·7 cm$^2$. The stroke volume correlated with valve area. There was no significant difference between the three groups for most of the other invasive variables (Table 1).

### *Electrocardiography*

The R amplitude criteria of left ventricular hypertrophy (Minnesota code 3.1 or 3.3) were fulfilled in 84% of the patients. One of the patients with a moderate stenosis had a normal electrocardiogram at rest. The remaining patients had left bundle branch block (four), signs of old infarction (two), pacemaker (one), or T wave abnormalities (seven).

### *Exercise test*

An exercise test was performed by 76 patients (84%) 37 of whom were in New York Heart Association functional class III or IV. There were no complications. The reasons for interruption of the exercise test were blood pressure reaction (36%), chest pain (29%), dyspnoea (34%), vertigo (3%), tiredness (26%), other (29%). Physical work capacity was reduced to below 80% of the reference value$^{20}$ in 95% of the patients. Figure 5 shows the relation of the work capacity to valve area and to the New York Heart Association functional classification. Sixty two patients (82%) had a subnormal blood pressure increase (n=33) or a blood pressure reduction (n=29) during the exercise test. Thirteen patients without a history of dizziness or syncope and with normal left ventricular ejection time had a subnor-

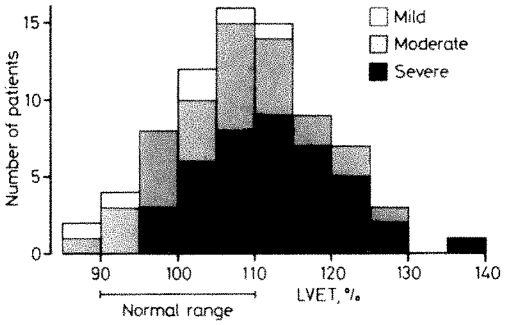

Fig. 6 *Left ventricular ejection time corrected according to Meiners*[11] *in relation to calculated aortic valve area.*

mal blood pressure increase or a blood pressure reduction with this test.

*Phonocardiogram and carotid pulse recording*

As the valve area decreased the maximum of the murmur tended to come later in systole (Table 2), but this resulted in a significant difference only between the group with severe and that with mild stenosis and only at the apex. The fourth sound was abnormal in 25% of the patients; this sign was equally common in all three groups. Only 5% of the patients had an abnormal third heart sound. The left ventricular ejection time, U time, and T time were significantly longer for the group with severe stenosis compared with the groups with moderate and mild stenosis (Fig. 6, Table 2).

*Echocardiography*

In all patients echodensity was increased in the aortic valve region. Left ventricular wall thickness was increased in 44 (90%) of the 49 patients in whom it

Table 2 *Findings at phonocardiogram and pulse curve registrations*

| | *Aortic stenosis* | *No* | *Mean* | *SD* | *Range* |
|---|---|---|---|---|---|
| QM2-A | Severe | 39 | 0·66 | 0·06 | 0·53–0·82 |
| | Moderate | 35 | * 0·63 | 0·07 | 0·48–0·77 |
| | Mild | 6 | 0·58 | 0·10 | 0·44–0·68 |
| QM2-B | Severe | 44 | 0·67 | 0·05 | 0·59–0·76 |
| | Moderate | 33 | 0·65 | 0·07 | 0·47–0·79 |
| | Mild | 6 | 0·65 | 0·11 | 0·45–0·78 |
| LVET (%) | Severe | 41 | 111 ** | 9 | 97–135 |
| | Moderate | 30 | ** 106 | 9 | 86–127 |
| | Mild | 6 | 100 | 9 | 89–112 |
| U time (ms) | Severe | 41 | 240 * | 27 | 190–300 |
| | Moderate | 30 | ** 225 | 25 | 180–280 |
| | Mild | 6 | 199 * | 25 | 170–250 |
| T time (ms) | Severe | 41 | 71 * | 17 | 39–120 |
| | Moderate | 29 | ** 62 | 16 | 35–106 |
| | Mild | 6 | 45 * | 14 | 35–70 |

QM2, fractional time of maximum of murmur in relation to electromechanical systole; A, apex; B, base; LVET, left ventricular ejection time, corrected according to Meiners.[11] U time and T time are rate corrected according to Bazett.[12]
$^{*}p < 0.05$, $^{**}p < 0.01$.

Table 3 *Echocardiographic findings*

| *Variable* | *Aortic stenosis* | *No* | *Mean* | *SD* | *Range* |
|---|---|---|---|---|---|
| LVIDed (mm) | Severe | 25 | 51 | 9 | 39–76 |
| | Moderate | 23 | 54 | 8 | 35–74 |
| | Mild | 4 | 66 | 10 | 52–73 |
| (IVSed + LVPWed)/2 (mm) | Severe | 25 | 15·2 | 2·3 | 12–20 |
| | Moderate | 21 | 14·3 | 2·0 | 11–19 |
| | Mild | 3 | 13·8 | 1·0 | 13–15 |
| Left ventricular mass (g) | Severe | 25 | 433 | 141 | 263–788 |
| | Moderate | 21 | 442 | 124 | 271–738 |
| | Mild | 3 | 532 | 178 | 370–722 |
| LAes (mm) | Severe | 39 | 41 | 7 | 27–58 |
| | Moderate | 31 | 42 | 7 | 31–61 |
| | Mild | 6 | 44 | 6 | 38–52 |

LVIDed, left ventricular end diastolic diameter; IVSed, septal end diastolic thickness; LVPWed, left ventricular posterior wall end diastolic thickness; LAes, left atrial end systolic diameter.

could be measured. The left ventricle was dilated to more than 55 mm in 19 (37%) of 52 cases (Table 3). There was no correlation between estimated left ventricular mass and valve area, nor between severity of aortic stenosis and left atrial size.

### *Radiography*

Aortic calcification was seen in 44 (90%) of 49 cases on the chest *x* ray in the group with severe, in 23 (68%) of 34 cases in the group with moderate, and in two (33%) out of six cases in the group with mild stenosis. The corresponding figures for calcifications on the cineradiography were 49/49 (100%), 33/34 (97%), and 5/5 (100%).

### *Coronary angiography*

Of 70 patients (77%) who suffered from chest pain 63 (90%) had coronary angiography. Seventeen (27%) of these had at least one coronary arterial stenosis reducing the luminal area by 70% or more. Single vessel disease was found in 10 patients, two and three vessel disease in five and two respectively. Of the remaining 21 (23%) patients without chest pain, 14 (67%) had coronary angiography and none had a stenosis.

## Discussion

Because the patients in this study were selected on account of their apparent need of operation, the frequency of particular symptoms or signs in them should not be taken as being representative of an unselected population of patients with aortic valvar disease. This applies especially to the group with mild stenosis. In four of the six patients in this group the non-invasive results did not indicate a severe stenosis and in one they were contradictory, but the patients were catheterised because of severe symptoms, exercise related dizziness or syncope or left ventricular failure in combination with a murmur of aortic stenosis.

Patients with aortic regurgitation were not excluded because aortic stenosis seldom occurs without any regurgitation in this age group. Patients who before catheterisation were judged to have predominant aortic regurgitation with minimal stenosis were, however, not included.

The severity of an aortic stenosis can be expressed as the pressure difference across the valve or as the calculated valve area.[18] With aortic regurgitation, the area is underestimated because the flow across the valve is greater than the forward stroke volume measured by the Fick method. Expression of aortic stenosis in terms of valve area does, however, give information about the degree of haemodynamic load imposed by the valve lesion.

### CLINICAL AND NON-INVASIVE FINDINGS

No relation was found between single symptoms and valve area; this accords with other studies.[21 22] It is not surprising since the symptoms of other disease—for example, coronary artery disease—may resemble those of aortic stenosis.

The non-invasive findings can be classified according to morphological changes in the aortic valve, haemodynamic effects of obstruction to flow, measures reflecting left ventricular hypertrophy, and of functional capacity.

### *Morphological changes in the aortic valve*

In 78% of the whole group and 90% of those with severe stenosis calcification was seen on the chest *x* ray. This is slightly less than was reported by Szamosi and Wassberg who found calcification in 91% of patients with aortic stenosis undergoing operation[23] but more than that reported by Nakamura *et al.*[6] Cineradiography was much more sensitive than the chest *x* ray, and detected calcification in 99% of our study group. Increased echodensity at the aortic valves was even more sensitive than cineradiography since it was detected in 100% of patients, although the severity of aortic stenosis could not be assessed from the extent of cusp separation (which was often undetectable). Therefore fluoroscopy and echocardiography are extremely useful because they can reliably suggest or rule out the possibility of aortic stenosis in the atypical case.[24]

### *Non-invasive measures of the obstruction to flow*

Late peak intensity of the systolic murmur is correlated with severity of aortic stenosis.[3 5 25] The peak intensity was, however, difficult to identify in our patients because there was considerable beat to beat variation, which was often due to irregular high intensity vibrations occurring within the murmur. In all patients except two, however, the murmur was most intense in late systole. A prolonged left ventricular ejection time and a slow rise of the systolic pulse wave is typically found in valvar aortic stenosis. An appreciable number of our patients, however, had a normal left ventricular ejection time. However, the left ventricular ejection time, the rate corrected upstroke time, and T time differed considerably in the three groups. The carotid pulse tracing is therefore a useful aid for estimating the severity of aortic stenosis in this age group too.[3 5 26]

### *Non-invasive variables reflecting left ventricular hypertrophy*

The frequency (84%) of electrocardiographic evidence of left ventricular hypertrophy was similar to that reported in other studies.[27] Only one patient

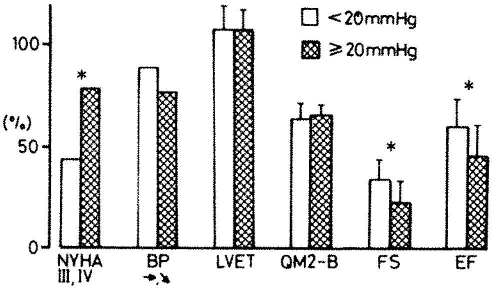

Fig. 7 *Comparison between patient groups with left atrial pressure < 20 and ≥ 20 mm Hg with regard to symptoms (New York Heart Association III or IV), blood pressure reaction at exercise test (BP), left ventricular ejection time (LVET), time of maximum systolic murmur in relation to electromechanical systole (QM2-B), fractional shortening (FS), and ejection fraction (EF) measured with M mode echocardiography.*

had a completely normal electrocardiogram. Left ventricular wall thickness was increased in 90% of the patients in whom it was possible to define the myocardial borders echocardiographically. This was, however, possible only in 54% of the patients. The frequency of echocardiographic left ventricular hypertrophy was similar to that observed by others.[28] Bennett's formula[29] for estimation of the degree of stenosis from the ratio of wall thickness to left ventricular cavity dimension was not applicable to our patients. It has been suggested that patients with severe aortic stenosis have an increased left atrial size.[30] This was not true in our patients.

### *Functional evaluation*

The exercise test was performed by 84% of the patients. Many were in New York Heart Association functional class III or IV; but with precautions, namely, frequent blood pressure recordings, and interruption of the test when blood pressure fell or dizziness or angina occurred, the tests could be performed safely. As with other observations[31 32] the exercise test gave additional information about the functional capacity. Eight patients in New York Heart Association class III or class IV had only a moderatly reduced work capacity (50–80% of the expected) while 12 patients in New York Heart Association class II had a work capacity below 50% of expected.

## FACTORS INFLUENCING THE NON-INVASIVE FINDINGS

The reason why combinations of non-invasive tests are needed for accurate prediction of severe aortic stenosis is because factors other than the degree of aortic valvar obstruction—notably medication, hypertension, left ventricular dysfunction, and coronary artery disease—will affect the measurement of single variables.

Patients treated by $\beta$ receptor blockade or diuretics or both and untreated patients did not differ in regard to the type of blood pressure reaction or the left ventricular ejection time. Arterial hypertension was equally distributed between patients with and without electrocardiographic signs of left ventricular hypertrophy. Hypertension had no demonstrable influence on the correlations between echocardiographic measures of left ventricular hypertrophy and aortic valve area. Genovese *et al* have reported that patients with aortic stenosis and hypertension have an earlier maximum of the systolic murmur than those without hypertension.[33] This was not the case in our patients.

To analyse the effect of left ventricular dysfunction we excluded patients with moderate to severe mitral regurgitation and compared the non-invasive findings in patients with a left atrial mean pressure of 20 mm Hg or more with patients with lower left atrial pressures (Fig. 7). Only New York Heart Association functional class, echocardiographic fractional shortening, and ejection fraction discriminated between the two groups. Thus in elderly patients it was difficult to determine whether symptoms such as dyspnoea or a reduced exercise tolerance were caused by the aortic stenosis, left ventricular dysfunction, or both.

Both coronary artery disease and aortic valve disease may produce angina. Our patients had a similar frequency of chest pain and coronary artery disease as earlier reported in middle aged patients with aortic stenosis. Coronary artery disease was not found in any patient without angina pectoris which accords with another report.[34] Hence the indication for coronary angiography in patients without angina is questionable.

To summarise, in elderly patients with aortic stenosis: (*a*) electrocardiography and chest *x* ray are useful for routine examination, and normal findings do not exclude severe aortic stenosis; (*b*) a late maximum of the systolic murmur is characteristic of severe aortic stenosis, even in patients with left ventricular dysfunction or hypertension; (*c*) in severe aortic stenosis the carotid pulse tracing is often abnormal, and to some extent the degree of abnormality correlates with the severity of stenosis; (*d*) there is evidence of left ventricular hypertrophy on the electrocardiogram in 80–90% of cases and by echocardiography in about 90% of those patients in whom satisfactory recordings are obtained; (*e*) echodense aortic valves with reduced motility are a reliable echocardiographic indicator of aortic valve disease, which is valuable in atypical cases and for the differentiation between subvalvar obstructions and aortic stenosis, but this investigation does not indicate the severity of the disease; (*f*) coronary artery disease without angina pectoris is very rare and the need for routine coronary angiography in this age group is therefore questionable; (*g*) the exercise test gives an objective measurement of the physical work capacity—an inadequate blood pressure reaction during exercise is a common finding; (*h*) when most findings point to severe aortic stenosis the absence of a single symptom or non-invasive sign does not exclude this diagnosis.

This study was supported by grants from the Swedish National Association against Heart and Chest Diseases, the County Council of Östergötland, and the Swedish Medical Research Council.

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# The need for invasive cardiological assessment and operation: viewpoint of a district general hospital

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SUMMARY The uptake of cardiac catheterisation and operation and of permanent pacemaker implantation in a district hospital in Surrey from 1979 to 1984 was studied prospectively. The 1982–84 figures for coronary artery operation indicated that 362 procedures/million population/annum were needed in the district. If patients with ≥New York Heart Association grade II angina only received operation the corresponding figure would have been 325. The national need for these procedures (464/million population/year) was estimated by correcting for the low standardised mortality ratio for ischaemic heart disease in the health district that was studied. Valvular heart disease accounted for 79 operations/million population/annum and permanent pacemaker insertion for 87 procedures/million population/annum. These figures underline the substantial shortfall in modern cardiac care in the United Kingdom.

The past two decades have seen substantial advances in both the techniques available to the cardiologist and in the scope of cardiac surgery. Information on the provision of cardiac surgery in the United Kingdom,[1] the United States,[2 3] West Germany,[4] and Australia[5] suggests that the United Kingdom is behind other industrialised nations in the provision of cardiological care. An estimate of the requirement for cardiological investigation and operation is needed to plan for health care resource allocation. There are, however, no data currently available in the United Kingdom to indicate the likely demand for these procedures as district hospital facilities become more fully developed. We report on a prospective six year study of the uptake of invasive investigative facilities and operation by a district hospital cardiac unit that was set up in line with the recommendations of the Joint Cardiology Committee.[6] The national need for these procedures was estimated by extrapolation after making some adjustment for regional variation in the prevalence of coronary artery disease.

## Patients and methods

### THE HEALTH DISTRICT

St Peter's Hospital, Chertsey, is the district hospital serving the North West Surrey Health District. The average population of the district during the period of the study (1979–84 inclusive) was 202 000. The proportion of those over retirement age was 17%. The figure for England and Wales as a whole is 18%.[7] The social class distribution of the population was skewed towards classes I and II. The standardised mortality ratio (SMR) for ischaemic heart disease (International Classification of Diseases 410–414) for the district was 0·78 and for valvar heart disease (International Classification of Diseases 393–398) it was 1·00.[8]

### THE LOCAL CARDIAC DEPARTMENT

The establishment of the non-invasive cardiac department at St Peter's Hospital has been reported elsewhere.[9] Facilities include computer assisted exercise electrocardiography, Holter monitoring, cross sectional echocardiography, and nuclear cardiology. There are four technicians. General practitioners are encouraged to refer all cardiological patients to the district hospital and more than 4000 outpatient appointments are made each year. Patients with unstable angina and recent myocardial infarction are admitted to the four bedded coronary

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Accepted for publication 6 January 1986

care unit which has approximately 550 admissions per annum. All patients within the hospital who require invasive cardiac assessment or operation are referred via the local department. Subsequent follow up is also performed locally.

### DIAGNOSTIC CATEGORIES

Since 1979 a register has been kept of all patients referred from the district hospital for cardiac catheterisation and operation. Information is thus available on age, symptom and risk factor status, medication, and the outcome of invasive investigation and operation. The term ischaemic heart disease in this paper includes chronic stable angina, unstable angina, myocardial infarction, and atypical chest pain requiring angiography to assist in diagnosis. Also included in this group are those patients with heart failure secondary to coronary artery disease and non-rheumatic mitral regurgitation associated with coronary artery disease. The term valvar heart disease includes aortic valve disease with and without coronary artery disease, chronic rheumatic heart disease, and valve operation after bacterial endocarditis. Conditions falling outside these definitions are grouped together as "other".

### SYMPTOMS AND TREATMENT

Symptoms were classified according to the New York Heart Association criteria.[10] Antianginal medication and its dosage were recorded and contraindications and side effects were noted. Treatment with two or more agents was considered to be an adequate trial of medical treatment.[11] Only data from the years 1982–84 were used to calculate the need for invasive investigation and coronary artery operation. This was when antianginal therapeutic regimens including $\beta$ blocking agents, calcium antagonists, and mononitrates became generally accepted and the early evidence of the long term benefits of operation were recognised.[12]

### INVASIVE DATA

Analysis of the left ventriculograms and coronary angiograms was based on the reports of the investigating cardiologists. The severity, number, and site of stenoses were noted on a graticule and the disease was classified as single, two vessel, two vessel with proximal left anterior descending stenosis, three vessel, or left main stem stenosis, according to the European Trial Criteria ($\geqslant 50\%$ stenosis).[12] The presence or absence of left ventricular impairment at angiography was also noted.

### REVIEW OF CATCHMENT

To take account of the fact that some patients were referred directly to a cardiac centre (usually the National Heart or Brompton Hospitals) by their general practitioners we sent a postal questionnaire to the 109 principals in general practice in the district. Those who did not reply were telephoned. Only two declined to cooperate. In 1983 the South West Thames Regional Authority reviewed the origin of all patients undergoing investigation and/or operation in the National Heart and Brompton Hospitals.[13] Thus there were accurate data on the number of patients living in the North West Surrey District who had coronary artery or valve operation in 1983 in these hospitals. These figures were assumed to be constant throughout the study period. We corrected for patients living outside the catchment area by excluding those who had home addresses outside the geographical catchment area at the time of referral.

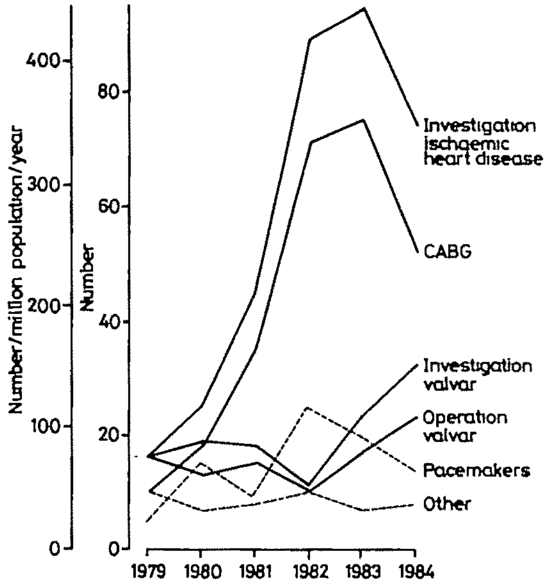

Fig. 1 *The total number of patients referred from the district cardiac unit 1979–84 for invasive investigation, operation, and pacemaker implantation. The inner scale of the ordinate represents the number of patients and the outer scale the number of patients per million population.*

## Results

Figure 1 shows the total number of patients referred from the district cardiac unit for invasive investigation and operation during 1979–84. These figures do not include corrections for cross boundary inflow or outflow. The number of patients referred and operated upon for ischaemic heart disease increased until 1983 and declined in 1984. Ten patients (six in 1983 and four in 1984) who underwent percutaneous transluminal angioplasty are included in these figures, which also include three re-operations. Five of the ten angioplasty patients came to coronary artery bypass within six months. There has been a slower increase in the rate of investigation and operation for valvar heart disease and for permanent pacemaker insertion. Miscellaneous procedures such as pulmonary embolectomy remain infrequent.

### ISCHAEMIC HEART DISEASE

The mean age of patients referred for coronary artery bypass operations increased from a mean (SEM) of 52 (1·5) years to 55 (1·0) years during the study period. The ratio of males to females varied but was approximately 6:1 overall. Despite the local policy not to refer smokers, 21% of patients said that they were smokers at presentation to the regional centre in 1979. This figure had fallen to 14% by 1984.

Forty seven per cent of all patients referred had New York Heart Association grade II or III angina and 25% had grade IV angina. Symptoms were less severe or absent in the remainder. Previous myocardial infarction had been documented in 46% of patients at the time of referral and 65% were found to have impaired left ventricular function at subsequent ventriculography. The waiting times for coronary angiography showed no consistent trend during the period. The mean waiting list time for angiography was 62 days and for operation it was 132 days. These not unfavourable waiting times, however, conceal very substantially longer periods, sometimes exceeding 18 months, for some patients. Urgent cases were usually accommodated. Three patients died on the waiting list for angiography. One had atypical pain and severe coronary artery disease at necropsy, one had New York Heart Association grade II, and one had grade III angina. Waiting time at death was one to four months. Four patients died on the waiting list for operation during the six year period. All had severe two or three vessel disease and had been waiting 1–20 months. There were two deaths within 24 hours of angiography (intractable ventricular fibrillation, myocardial infarction).

Figure 2 shows the distribution of coronary artery disease in the patients investigated. Figure 3 shows the angiographic findings in relation to symptoms and treatment. Several patients had angiographically severe lesions despite mild symptoms. The percentage of patients invasively investigated who proceeded to operation increased during the study period from 62% in 1979 to 80% in 1983 and declined to 70% in 1984. The overall 28 day mortality fell from 6% in 1981 to 3% in 1983.

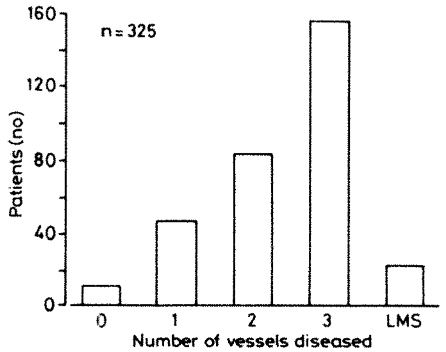

Fig. 2 *The distribution of coronary artery disease in the patients investigated 1979–84. The abcissa records the number of vessels affected or left main stem (LMS). European Coronary Surgery Study Group criteria were used.*[12]

### VALVAR HEART DISEASE

The mean (SEM) age of patients undergoing surgery for valvar heart disease remained constant during the study period at 62 (2·5) years; the sexes were equally represented. The waiting list times resembled those experienced by patients with ischaemic heart disease. In 57% of the 119 referrals aortic valve disease was present and 13% of these had co-existent coronary artery disease that required grafting. All patients in the latter group had angina pectoris. The operative mortality was 5·9% overall for aortic valve replacement, including those who

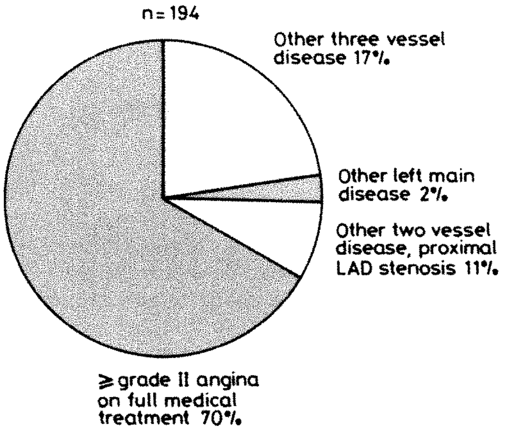

Fig. 3 *Distribution of angiographic findings in relation to symptoms and treatment based on 1982–84 figures only (see text). Twelve patients with inoperable coronary artery disease were excluded. LAD, left anterior descending artery.*

Table 1 *Miscellaneous procedures classified as "other" (see text)*

| *Other procedures* | *1979* | *1980* | *1981* | *1982* | *1983* | *1984* | *Total* |
|---|---|---|---|---|---|---|---|
| Electrophysiological study | 5 | 1 | 2 | 0 | 3 | 2 | 13 |
| "Cardiomyopathy" | 1 | 4 | 0 | 1 | 2 | 3 | 11 |
| Congenital heart disease | 4 | 1 | 0 | 4 | 0 | 1 | 10 |
| Aortic dissection | 1 | 1 | 1 | 2 | 0 | 0 | 5 |
| Pulmonary embolism | 0 | 0 | 3 | 0 | 0 | 1 | 4 |
| Pericardial disease | 0 | 0 | 2 | 1 | 1 | 1 | 5 |
| Primary pulmonary hypertension | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
| Total | 11 | 7 | 8 | 8 | 6 | 9 | 49 |

had coronary artery bypass grafts. There was one death after cardiac catheterisation (concealed haemorrhage from an iliac vessel). Two patients died on the waiting list for operation (heart failure, suicide).

### PERMANENT PACEMAKER INSERTION AND MISCELLANEOUS PROCEDURES

Figure 1 shows the number of permanent pacemaker insertions each year. Table 1 gives the referrals for miscellaneous cardiological conditions. The numbers are too small for further analysis.

### GENERAL PRACTITIONER SURVEY

Sixty two practitioners providing primary health care to 124 684 patients had not referred patients directly out of the district. One hundred and two coronary artery bypass procedures were performed on patients registered with these general practitioners during 1982–84. This corresponds to 273 operations per million population per annum. The remaining 45 practitioners said that some of their patients had been referred out of the district. The reasons given for direct referral included delay in obtaining outpatient appointments at the district hospital, previous experience of delays at the referral centres used by the district hospital, and referral by employment health schemes. Few of the general practitioners had accurate records of the numbers of patients referred or their fate. Estimates ranged from none to 15 operations per annum. Nevertheless 73 of the 95 881 patients on the lists of these practitioners came to coronary artery operation through the district cardiac unit, either after emergency admission or because the district facilities had been used on that occasion. This group of practitioners accounted for 254 operations per million population per annum. This figure excludes patients referred directly out of the district.

When the general practitioners were ranked according to the number of patients registered with them who came to operation during the study there was a wide variation. Table 2 gives the apparent need for operation on patients of the "top scoring" 50% or 25% of the general practitioners expressed as the number of operations per million population per annum.

### NATIONAL HEART AND BROMPTON HOSPITALS SURVEY

During 1983 eight patients underwent coronary artery bypass grafting at the Brompton and National Heart Hospitals and two underwent valve operation.[13] Four patients came from outside the catchment area during 1982–84 and underwent coronary artery bypass grafting and during 1984 six came to

Table 2 *Calculation* of the requirement for coronary artery bypass grafting (CABG)*

| *Data* | *CABG procedures*† | *Valve operations*‡ *(per million population per annum)* |
|---|---|---|
| (*a*) North West Surrey Health District | 327 | 79 |
| (*b*) Corrected for cross boundary flow | 362 | 79 |
| (*c*) Corrected for regional variation in SMR (see text) | 464 | 79 |
| (*d*) Corrected to include only symptomatic (NYHA grade II) patients on full treatment (see text) | 325 | — |
| (*e*) Top 50th percentile of GPs (see text) | 643 | — |
| (*f*) Top 25th percentile of GPs (see text) | 1716 | — |

*Based on (*a*) St Peter's Hospital figures; (*b*) as (*a*) but corrected for cross boundary flow; (*c*) as for (*b*) but corrected for regional variation in standardised mortality rate (SMR); (*d*) based on (*c*) but including only patients with New York Heart Association (NYHA) grade II or more angina on two or more drugs; (*e*) based on (*c*) and the need for surgery judged by the activities of the top 50th and top 25th percentile of general practitioners for referrals.

†Based on 1982–84 figures (includes percutaneous transluminal coronary angioplasty and re-operations).

‡Based on 1979–84 figures.

valve operation. Cross boundary flow was thus balanced for valve operation but a small adjustment was needed for coronary artery bypass procedures (see Table 2).

## Discussion

There have been no previous detailed reports of the requirement in the United Kingdom for invasive cardiological investigation and operation nor has the operational experience of a district hospital cardiological unit been similarly reported. Fry in his general practice survey found an incidence of angina of 0·39% per annum.[14] The Research Committee of the Northern Regional Faculty of the Royal College of General Practitioners suggested that about 300 patients per million population per annum developed "severe" angina. This was not based on information about treatment or angiographic findings.[15] The recent consensus statement that the United Kingdom required a provision for 300 coronary artery bypass graft operations per million population per annum was anecdotal.[16]

Our data show a rise and latterly some decline in the number of patients operated upon for ischaemic heart disease while no similar trend has been seen in operation for valvar heart disease. There are several explanations for this. Initially there may have been a backlog of referrals. The publication of the findings of the European Coronary Surgery Study Groups in 1982 suggesting that operation enhanced survival in three vessel and two vessel disease with a proximal left anterior descending coronary artery stenosis, irrespective of symptoms,[12] influenced decision making. More recently the Coronary Artery Surgery Study has questioned this.[17] The local requirement expressed as procedures per million population per annum is 362 for ischaemic heart disease (and includes percutaneous transluminal coronary angioplasty and re-operations), 79 for valve operation, 87 for permanent pacemaker insertion, and 40 for miscellaneous conditions. The figure for coronary artery bypass grafting may be adjusted if it is assumed that the standardised mortality ratio for North East Surrey Health District (0·78) reflects the local prevalence of ischaemic heart disease. If this is the case the national need for coronary artery bypass procedures increases to 464 when the local need is divided by the standardised mortality ratio.

There was much variation in the number of patients referred by general practitioners. Possible explanations include chance, age distribution of patients, and the general practitioner's attitude towards operation. By examining the top 50th and the top 25th percentile of practitioners we estimated the effect if all general practitioners had referred patients at the same rate. These estimates (Table 2) may reflect more closely the true need in the community for coronary artery procedures and are closer to the provision for operation in other countries. The most recently available data suggest a national provision in Australia of 420[18] and in the United States of about 800 coronary procedures per million population per annum.[3]

Indications for coronary artery operation include angina resistant to medical treatment and the possibility of improving survival. The three major randomised trials that have been reported, however, are to some extent contradictory.[12 17 19] Hampton has reviewed them and he concluded that disabling angina may be the only indication for operation.[20] If so, the current United Kingdom provision (excluding percutaneous transluminal coronary angioplasty) at 171[21] is approximately one half of the 325 operations that our data suggest are required for symptoms alone. If operation is also offered for enhancement of survival in left mainstem stenosis, three vessel disease, and two vessel disease with a proximal left anterior descending artery stenosis[12 19] the present national provision is less than a third of that required. To some extent the need for coronary artery operation reflects the policy of the referring centre. Thus in the North West Surrey District all patients in whom coronary artery disease is overt (that is after myocardial infarction) or suspected on the basis of symptoms undergo non-invasive evaluation if they are aged ≤60 years. Assessment above this age is more selective.

The North West Surrey District requires 79 operations per million population per annum for valvar heart disease. This compares with the total United Kingdom figure (76)[1] and that of South Australia (74)[22] both expressed in the same units. There was a modest growth in the uptake of these procedures between 1979 and 1984 but it seems unlikely this will increase further unless the predicted change in the age structure of the population brings a concomitant increase in the need for aortic valve operation which is the predominant problem.

Finally the figures for permanent pacemaker implantation (87 precedures per million population per annum) compare with the national figures (75) which are among the lowest in the Western World.[23] We think that this in part represents a conservative approach, notably to sinoatrial disease, at the regional centre.

Recently there has been increasing emphasis on the cost effectiveness of coronary artery procedures both in economic terms and in terms of the enhancement of quality of life.[16 24] It is, however, salutory to recall that nine patients (discounting the suicide) died on the waiting list for investigation or operation. This represents 2·3% of all those subsequently undergoing operation and had regional facilities been adequate these deaths could have been avoidable. Attention has already been drawn to the inadequacy of district cardiological services,[25] the inadequate provision of regional services,[1] and the poor use of available resources.[26]

## Conclusion

Our data suggest that at best current provision for coronary artery surgery in the United Kingdom caters for between one third and one half of the number of patients who might benefit from it. A more aggressive pattern of referral from general practitioners could increase this requirement still further. Operation for valvar heart disease is more in line with need, although this may not be true of permanent pacemaker implantation.

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*Br Heart J* 1986; 55: 494–6

## *Case reports*

# Echocardiographic demonstration of pulmonary valve endocarditis associated with congenital ventricular septal defect

JOHN CHAMBERS,* GRAHAM LEECH

*From the Department of Cardiology, St George's Hospital, London*

SUMMARY A 38 year old woman previously known to have a heart murmur presented with malaise and bloodstained sputum. Echocardiographic examination showed a subpulmonary ventricular septal defect and probable vegetations on the pulmonary valve, and blood cultures grew *Escherichia coli*. She made a full recovery after 6 weeks' antibiotic treatment.

The pulmonary valve is rarely affected by subacute bacterial endocarditis and it is the most difficult of the four cardiac valves to visualise by echocardiography. Consequently there are few reports of the echocardiographic demonstration of pulmonary valve vegetations. We present an unusual case in which pulmonary valve vegetations were found in association with a jet lesion from a subpulmonary ventricular septal defect.

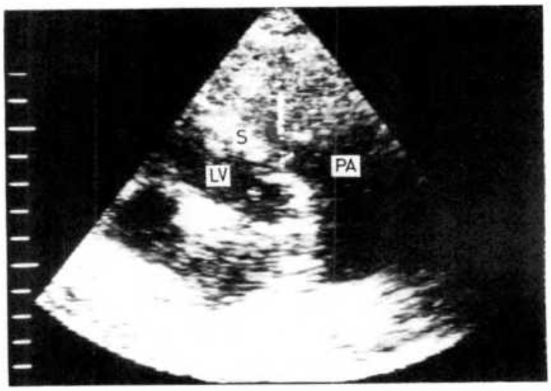

Fig. 1 *A parasternal angled short axis section just below the aortic valve. The image quality is poor because a 2·25 mHz transducer was used for subsequent Doppler echocardiographic recordings, but the subpulmonary ventricular septal defect can be seen (arrowed). The Doppler sample is positioned in the right ventricular outflow tract below the pulmonary valve. S, interventricular septum; LV, left ventricle; PA, pulmonary artery.*

## Case report

A 38 year old Greek woman with a three month history of general malaise and myalgia and a cough productive of bloodstained sputum who had been told she had a congenital heart lesion travelled to the United Kingdom to seek medical advice.

On examination she was generally well with no stigmata of subacute bacterial endocarditis. Her blood pressure was 120/90 mm Hg with a heart rate of 72 beats/min. There was a loud pansystolic murmur with an associated thrill at the left sternal edge and a soft early diastolic murmur over the pulmonary area that was best heard in inspiration. Her chest *x* ray showed an enlarged cardiac shadow and pulmonary plethora, but no evidence of pulmonary emboli. The electrocardiogram was within normal limits. A cross sectional echocardiogram showed a ventricular septal defect below the pulmonary valve (Fig. 1), and the presence of a high-velocity jet across this lesion was confirmed with pulsed Doppler echocardiographic examination. The pulmonary valve was thickened and there was a separate echodense mass associated with the valve but which moved independently of it. This was interpreted as a vegetation (Fig. 2). There was Doppler evidence of pulmonary regurgitation. The other valves all appeared to be normal. She had a mild normochromic normocytic anaemia of 11·3 g/dl and a white blood cell count of $10\cdot1 \times 10^9$/l. Two blood cultures out of six grew *Escherichia coli*. She was obliged to return immediately to Greece, where she was treated with

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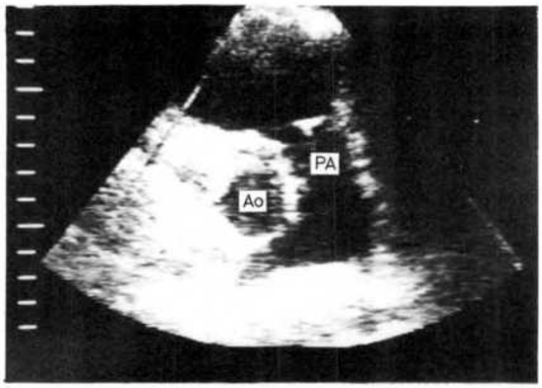

Fig. 2 *Parasternal short axis section at the level of the pulmonary valve. The pulmonary cusps are abnormally thickened and there is an echodense mass attached to one of them. Ao, aorta; PA, pulmonary artery.*

streptomycin and penicillin for 40 days and made a full recovery. Repeat blood cultures were negative.

## Discussion

The right heart valves are involved in only about 5% of all cases of endocarditis.[1] It has been suggested that this is due partly to the relatively low incidence of predisposing congenital defects on the right side of the heart and partly to the lower risk of endothelial damage because of lower intracardiac pressures.[2] Thus, infections on normal right sided valves are generally due to virulent organisms, or as a result of heavy inoculations from contaminated intravenous injections, notably in drug addicts.

*Staphylococcus aureus* is the organism most commonly found in pulmonary valve endocarditis. α haemolytic streptococci, and several less common organisms, such as *Pseudomonas,* are also found.[3-5] *Escherichia coli,* as in this case, is rare but has been reported before.[6 7]

For reasons that are unexplained, the pulmonary valve is affected in 18–25% of cases of gonococcal endocarditis.[8 9] With this exception, subacute bacterial endocarditis rarely affects the pulmonary valve even in cases in which there is gross infection of other right sided structures. In Johnson *et al's* review of subacute bacterial endocarditis in children, the pulmonary valve was involved in only five of 149 cases.[10]

The risk of endocarditis on the pulmonary valve is increased in the presence of a congenital abnormality or with acquired endothelial damage. The risk of endocarditis in congenital pulmonary stenosis has been estimated to be 0·2 cases per 1000 patient-years.[11] Pulmonary endocarditis has also been reported in Fallot's tetralogy.[12] Indwelling catheters can cause endothelial damage; in Rowley *et al's* study of 55 patients dying after right heart catheterisation, three had vegetations on the pulmonary valve.[6] The endothelium can also be damaged by a high velocity blood jet. In Gersony and Hayes's series, five patients had subacute bacterial endocarditis associated with a ventricular septal defect, two with vegetations around the margin of the defect and three with vegetations on the aortic valve, one of whom had additional lesions on the tricuspid and pulmonary valves.[11] Bain *et al's* study of right sided endocarditis included only one patient with a ventricular septal defect, who had vegetations at the sites of impact of jet lesions on the tricuspid valve and in the right ventricle.[13] Endothelial damage was most probably the disposing lesion in our case, in which the ventricular septal defect was situated just below the pulmonary valve.

The paucity of echocardiographic reports of pulmonary endocarditis results partly from the rarity of the condition and partly from difficulty in visualising the pulmonary valve. M mode recordings have demonstrated a shaggy appearance of the valve in diastole, with or without prominent systolic fluttering.[14-16] The few cross sectional echocardiographic studies have shown flail leaflets and direct visualisation of vegetative masses.[7 14 17] We believe that our case is the first in which an associated ventricular septal defect has been visualised by echocardiography. There is, however, a report of the echocardiographic diagnosis of pulmonary endocarditis where a small ventricular septal defect was subsequently shown at operation.[18]

Subacute bacterial endocarditis must be diagnosed on clinical and bacteriological grounds, but echocardiography is valuable in detecting associated valve lesions. Modern echocardiographic machines can detect vegetations with diameters of >2–3 mm. The addition of Doppler echocardiography provides a highly sensitive method for detecting regurgitant lesions. We found that the technique demonstrated the presence of pulmonary regurgitation and confirmed the site of the ventricular septal defect in a case in which the cross sectional images were only of moderate quality.

We are grateful to Dr Aubrey Leatham for permission to report his patient and to Dr John Kostarelos who provided details of the follow up.

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*Br Heart J* 1986; 55: 497–9

# Echocardiographic demonstration of free wall vegetative endocarditis complicated by a pulmonary embolism in a patient with ventricular septal defect

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*From the Department of Clinical Echocardiography, Thoraxcenter, Erasmus University and University Hospital Dijkzigt, Rotterdam, The Netherlands*

SUMMARY A defect in the muscular part of the interventricular septum in a 19 year old man was complicated by infective endocarditis caused by *Staphylococcus aureus*. The lesion was a large right ventricular free wall vegetation which embolised to the lungs. The vegetation was displayed by cross sectional echocardiography, which also confirmed the clinical diagnosis of ventricular septal defect. This case confirms the concept that the jet stream causes endocarditis at its point of impact. After six weeks' treatment with antibiotics the ventricular septal defect was repaired at operation.

Infective endocarditis is a rare complication of ventricular septal defects. Its incidence is estimated to be 2·2 per 1000 patient-years.[1 2] Various sites may be involved—the tricuspid and pulmonary valves, the right side of the septal defect opening, less commonly the left side of the defect, and the site of impact of the jet stream on the right ventricular free wall (jet lesion). We report a patient with a large right ventricular free wall vegetation that was complicated by pulmonary embolism.

## Case report

A 19 year old man who was known to have a cardiac murmur since birth, became ill and complained of a sore throat, malaise, and anorexia with a 5 kg weight loss. He had a temperature up to 40°C. His general practitioner prescribed antibiotics. He remained febrile and some days later he was referred to our department by his community hospital. On physical examination his temperature was 38·7°C, pulse rate 106 beats/min, and blood pressure 120/70 mm Hg. A grade 4/6 pansystolic murmur was heard along the left sternal border. The liver and spleen were not palpable. Neurological examination and fundoscopy were normal and there were no other peripheral signs indicative of endocarditis. Chest *x* ray and electrocardiogram were normal. Two blood cultures grew penicillin resistant *Staphylococcus aureus*. Treatment with oxacillin and gentamicin was started, his clinical condition improved, and the fever subsided in a week.

Echocardiography clearly showed a defect in the muscular part of the interventricular septum (Fig. 1a and b) and a large vegetation on the right ventricular free wall (Fig. 1c). On two subsequent echocardiographic examinations one and two weeks later the appearance of the vegetation remained unchanged. Four days after the third echocardiogram the patient suddenly experienced pleuritic pain on the right side. Echocardiography was repeated and the vegetation was no longer present (Fig. 1d). A radioalbumin scan of the lungs (Fig. 2) showed a right basal perfusion defect which was not present on the lung scan made two weeks earlier. The patient, however, did not develop dyspnoea, cough, haemoptysis, fever, or other clinical signs of pulmonary embolism, and the chest *x* ray remained normal.

After he had completed a six week antibiotic course he underwent surgical closure of the ventricular septal defect. The surgeon did not find any infective lesions near the ventricular septal defect and there were no vegetations on the right ventricular free wall. The pulmonary and tricuspid valves were normal.

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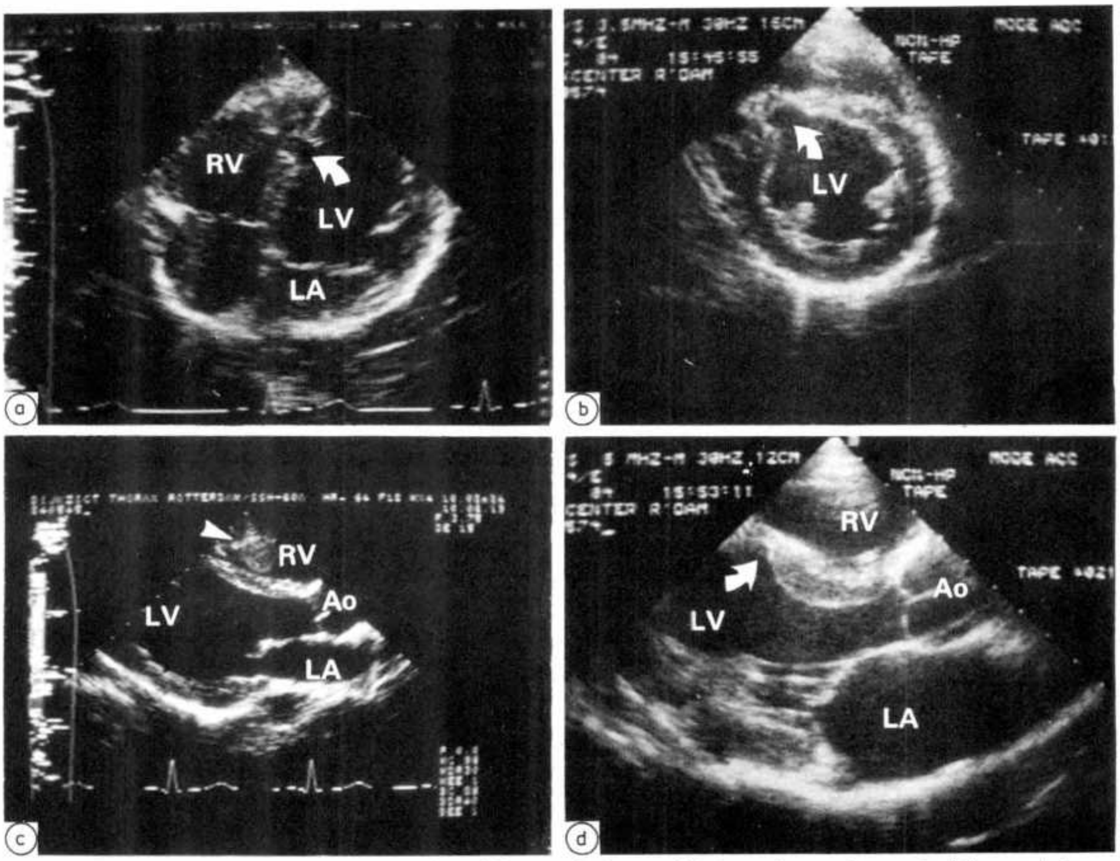

Fig. 1 *Cross sectional echocardiograms in a patient with a ventricular septal defect and vegetation on the right ventricular free wall. The defect in the muscular part of the interventricular septum is seen in the apical four chamber view (a) (arrow), and in the parasternal short axis view (b) (arrow). In the parasternal long axis view (c) the arrow points to a large right ventricular free wall vegetation, which had disappeared three weeks later (d). RV, right ventricle; LV, left ventricle; Ao, aorta; LA, left atrium.*

## Discussion

Infective endocarditis continues to be a serious risk in patients with congenital heart disease. Despite improved antibiotic treatment and prophylactic measures mortality is considerable.[1-3] The advent of cross sectional echocardiography is a major advance.[4-6] In our patient it confirmed the clinical diagnosis of a ventricular septal defect and showed the right ventricular vegetation. Apart from the ventricular septal defect no other lesions of the endocardium were found. We therefore must presume that the vegetation on the right ventricular free wall was the only abnormality. This case confirms the concept that the jet stream causes endocarditis at its point of impact. Because it was felt that there was a risk of recurrent endocarditis on the jet lesion, the patient underwent closure of the ventricular septal defect. Operation was performed on the basis of the cross sectional echocardiographic findings without

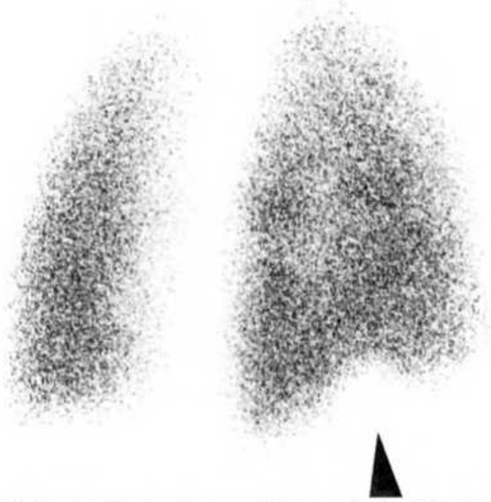

Fig. 2 *Radioalbumin scan of the lung in the right posterior oblique view. The arrow points at a right basal perfusion defect.*

preoperative cardiac catheterisation. This case also illustrates that embolisation of large vegetations to the lungs can pass almost unnoticed.

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# Proceedings of the British Cardiac Society

THE 65TH ANNUAL GENERAL MEETING of the British Cardiac Society was held at the University of York on Wednesday and Thursday, 2 and 3 April 1986. The President, D G JULIAN, took the Chair during private business.

The following were elected to the British Cardiac Society.

*New Ordinary Members:* J Bayliss (Buckinghamshire); R M Bini (Liverpool); R S Clark (Dundee); A J Cowley (Nottinghamshire); P A Crean (London); J C P Crick (London); W Culling (Bristol); K D Dawkins (London); A Fenech (Glasgow); T H Foley (Surrey); C J Foster (Manchester); K A A Fox (Cardiff); A G Fraser (Glamorgan); D J M Keenan (Manchester); C A Kekwick (Devon); J N Leverment (Leicester); P Lynch (Hampshire); D G McDevitt (Dundee); C G A McGregor (Newcastle); B Mittra (Sunderland); O J M Ormerod (Cambridge); W J Penny (Cardiff); J W Pidgeon (Merseyside); A P Rae (Glasgow); D R Ramsdale (Merseyside); M R Rees (Leeds); C J Reid (London); E Rowland (London); J M Rowley (Nottinghamshire); S Saltissi (Liverpool); M Varma (Fermanagh).

*New Corresponding Member:* K I Shine (Los Angeles).

*New Extraordinary Members:* J M Barber, H H Bentall, J F Goodwin, C B Henderson, D Mendel, E G Wade, W Whitaker.

*Resignations:* K Bloor, I M Hill, F S Jackson, R B Milstein.

*Death:* F Szekely.

*Elections*

E Sowton, President-Elect; J Coltart elected Secretary; D J Parker elected Treasurer; R H Swanton elected Assistant Secretary; M Joy and T Treasure elected to Council.

## Abstracts of papers

### Arrhythmias before and after anatomical correction of transposition of the great arteries

R Martin, Rosemary Radley-Smith, M H Yacoub
Harefield Hospital, Harefield, Middlesex

Ninety two patients were studied after anatomical correction of tranposition of the great arteries. Fifty four patients underwent primary correction, and 38 patients had two stage correction. Forty one patients had 24 hour ambulatory electrocardiograph recordings performed before any operative procedure. Thirty four (83%) patients showed sinus rhythm alone, one (2·4%) showed infrequent supraventricular extrasystoles, one (2·4%) showed a short episode of atrial fibrillation, five (12·2%) showed modified Lown grade 1 ventricular extrasystoles, and one (2·4%) showed an episode of ventricular tachycardia. Thirty one recordings in 20 patients after the first stage of a two stage repair showed no significant change in the frequency of any arrhythmias. No cases of late symptomatic arrhythmia or arrhythmia associated death occurred during a mean of 3·1 years follow up. Recordings immediately before discharge from hospital were performed in 47 patients. Supraventricular extrasystoles were seen in 13 (28%) patients and ventricular extrasystoles in 20 (42·5%), of which 14 (29·8%) were Lown grade 1 and six (12·8%) were Lown grade 3. One patient was in atrial fibrillation and one had paroxysmal atrial flutter. The latter patients required short term treatment with amiodarone. Sixty five recordings in 56 patients between three and 60 months after correction have demonstrated a low incidence of serious arrhythmias—38 (58%) showed sinus rhythm alone, 16 (25%) infrequent supraventricular extrasystoles, and 13 (20%) ventricular extrasystoles (11 Lown grade 1, one grade 3, and one grade 4). One early patient developed complete heart block postoperatively. In conclusion, there is a low incidence of important arrhythmias and late death after anatomical correction.

### Natural history and prognosis of fetal tachycardias

E J Ladusans, Dianne Crawford, Lindsey Allan, M Tynan, P V L Curry
Guy's Hospital, London

Fetal tachycardia was diagnosed by echocardiography in 13 patients who have now been followed up for a mean of 2·9 years (range 1·1–3·8). Average gestational age at diagnosis was 35 weeks (range 32–38). Atrial flutter (AF) was found in six patients (four with hydrops fetalis), atrial tachycardia (AT) in two, and paroxysmal supraventricular tachycardia (SVT) in five (two hydropic). Cardiac structure was normal in all cases. To control ventricular rate (that is, below 200 beats/min) 11 received prenatal treatment with digoxin and two of these required verapamil in addition. One neonate with severe hydrops and SVT died shortly after premature delivery at 36 weeks, despite postnatal attempts to control tachycardia. All patients were treated with digoxin at birth. All six with AF reverted to sinus rhythm (five before delivery) and this has been maintained. In four children with AF, treatment has been withdrawn without relapse (shortest follow up 3·1 years). Amiodarone was used successfully to control refractory AT in one baby; unfortunately she died at 2 years from pneumococcal meningitis. Digoxin was withdrawn from the other child with AT, who has now been free from attacks for 3·2 years. Of four children with SVT, treatment has been stopped without recurrence of tachycardia in two. Two children remain on digoxin; one required the addition of verapamil to control breakthrough SVT, the other is symptom free (at 2·6 and 1·6 years respectively). Aggressive intrauterine treatment of fetal tachycardia may prevent fetal hydrops, premature delivery, and neonatal death. The prognosis for rhythm control after birth is excellent.

## Ventricular septal defect and pulmonary hypertension (PHT): a long term follow up study

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To assess the long term efficacy of closure of ventricular septal defect (VSD) with PHT, 27 patients who were aged 3–12 years at operation were followed up for 19–27 years. All had large VSD, systemic level pulmonary artery pressure, and an overall left to right shunt, and 25 had a pulmonary arteriolar resistance of $\geqslant 8$ units. All patients were repeatedly examined clinically and by ECG and chest *x* ray and had at least two postoperative cardiac catheterisations with measurement of pulmonary arteriolar pressure at rest and on effort. Most patients had respiratory function tests, two stage exercise testing, 24 hour Holter monitoring, and cross sectional echocardiograms. In 1975 all were symptom free, very active, and had normal respiratory and exercise tests. However, only four had normal resting pulmonary artery pressure and in 16/16 this was abnormally raised on effort. By 1985 six patients had died (aged 17–32 years, and 14–21 years after operation) and three patients had symptoms. The other patients were symptom free and two women had children. The patients died in severe right heart failure within five years of first symptoms. Increasing heart size on chest *x* ray and cross sectional echocardiographic evidence of right ventricular dilatation and pressure overload were bad prognostic features preceding symptoms. Predictably the patients who died had severe PHT; however, three patients with severe PHT remain symptom free.

The patients had an excellent quality of life while they were symptom free but rapidly deteriorated once symptoms developed. The group as a whole may not be living as long as reported cases of Eisenmenger syndrome. In many cases pulmonary vascular disease appeared to continue to progress postoperatively in these patients who were all over two years of age when their large VSD was closed.

## Membranous supravalvar mitral stenosis: a potentially curable form of congenital heart disease

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Failure to differentiate membranous supravalvar mitral stenosis from isolated mitral valve stenosis may result in undue delay of operation because the likelihood of mitral valve replacement is high in mitral valve stenosis. Fourteen patients who had operation for membranous supravalvar mitral stenosis between 1978–85 were reviewed in an attempt to clarify specific echocardiographic features which might facilitate early diagnosis. Ages ranged from six weeks to 13 years. Associated lesions included ventricular septal defect (7), left superior vena cava (6), coarctation (5), subaortic stenosis (3), and atrial septal defect (1). Twelve patients had the membrane excised, and two patients with associated mitral valve stenosis required valve replacement. There were no operative deaths. Review of preoperative cross sectional echocardiograms which were available in 11 patients allowed retrospective diagnosis of membranous supravalvar mitral stenosis in 10 patients. Membranous supravalvar mitral stenosis had been recognised in only five of these preoperatively. There were two types of membranous supravalvar mitral stenosis: in seven patients the membrane was adherent to the valve and visible only in isolated diastolic frames. In the second type (three patients) there was clear separation between the membrane and valve leaflets in diastolic frames with systolic apposition of the valve leaflets and the membrane. Of 11 patients followed for > 1 year nine are alive. Eight are symptom free and seven have no evidence of left ventricular inflow obstruction. Patients with evidence of left ventricular inflow obstruction should have extensive cross sectional echocardiographic evaluation to detect membranous supravalvar mitral stenosis which may be amenable to operation without valve replacement.

## Chronic enalapril treatment reduces myocardial noradrenaline response to exercise in heart failure

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In congestive heart failure exercise tolerance and mortality are related to sympathetic activity. Angiotensin converting enzyme inhibitors may reduce the arrhythmias which contribute to mortality, perhaps by reducing sympathetic drive as reflected by plasma noradrenaline concentrations or myocardial noradrenaline release. The effects of treatment for six weeks with enalapril (20 mg/day) or placebo were investigated in a double blind crossover study of 14 men with congestive heart failure refractory to continuing digoxin and diuretic treatment. Eleven had ischaemic heart disease and three had congestive cardiomyopathy; the radionuclide ejection fraction was 20 (2) (mean (SE)). Exercise tolerance was assessed by the symptom limited duration of a standard protocol bicycle test. At peak exercise, enalapril compared with placebo reduced myocardial noradrenaline release by 88% from 92·5 (40·2) ng/min ($p < 0.05$), arterial noradrenaline by 3% from 1345 (187) pg/ml (NS), and coronary sinus flow by 16% from 240 (22) ml/min (NS). At rest, enalapril reduced these variables respectively by 55% from 20·2 (22·6) ng/min, by 1% from 871 (222) pg/ml, and by 6% from 142 (14) ml/min (all NS). Exercise tolerance was not significantly altered (−6% from 615 (77)s), but the double product at peak exercise was reduced by 21% from 21 292 (1758) mm Hg/s ($p < 0.05$). Transmyocardial arteriovenous oxygen difference was reduced by 12% from 14·2 (0·6) ml/dl ($p < 0.05$) and myocardial oxygen consumption by 26% from 35·2 (5·0) ml/min (NS).

This study provides direct evidence that chronic enalapril treatment reduces myocardial sympathetic stimulation during exercise in association with reduced myocardial workload.

## Haemodynamic effects of frusemide in the presence and absence of angiotensin converting enzyme inhibitors

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Angiotensin converting enzyme (ACE) inhibitors are usually prescribed with diuretics in patients with heart failure yet little is known about their interaction especially in relation to renal and cardiac function. We measured glomerular filtration rate (GFR), renal blood flow, and plasma volume radioisotopically, cardiac output by Doppler echocardiography, and serum and urine composition over six hour periods in twelve patients with cardiac failure on a fixed sodium and potassium intake, before and after frusemide (80 to 120 mg) and after one week of enalapril 10 mg daily. Enalapril alone increase cardiac output (3·0 (1) to 3·4 (1) l/min; $p < 0.05$) and reduced mean blood pressure slightly (90 (5) to 85 (4) mm Hg; $p < 0.01$). Renal blood flow rose (424 (202) to 494 (225) ml/min; $p < 0.08$) but GFR did not change (70 (27) and 69 (27) ml/min); consequently the filtration fraction fell (33 (14) to 26 (6)%; $p < 0.05$). With frusemide the addition of enalapril also increased cardiac output (3·1 (1·1) to 3·6 (1·0) l/min; $p < 0.01$) and reduced blood pressure (87 (5) to 79 (4) mm Hg; $p < 0.001$). Renal blood flow increased to a greater extent (463 (216) to 579 (211) ml/min; $p < 0.02$) but GFR declined (70 (27) to 63 (26) ml/min; $p < 0.001$) so that the filtration fraction fell markedly (30 (9) to 19 (5)%; $p < 0.001$). Enalapril without frusemide had no effect on urine volume but reduced the diuretic response to frusemide from 1·21 per 6 hours to 0·81 ($p < 0.001$). Plasma volume increased (3·4 to 3·7 l; $p < 0.02$) and body weight by 1·2 (0·5) kg over the one week treatment period. Enalapril inhibited the increases in angiotensin II, aldosterone, and noradrenaline induced by frusemide. ACE inhibitors appear to unmask the renal vasodilator effects of frusemide.

The reduced filtration fraction suggests that the increase in renal blood flow after ACE inhibitors is due to a reduction in angiotensin II mediated efferent arteriolar constriction which is enhanced by stimulation of the renin angiotensin system by potent diuretics leading to an accentuation of the renal effects of ACE inhibitors.

## Absorption of intramuscular human recombinant tissue type plasminogen activator (rt-PA) facilitated by methylamine: potential applications for coronary thrombolysis

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Expeditious administration of intramuscular (im) t-PA after infarction may maximise salvage of the myocardium with minimal systemic proteolysis. We have previously induced coronary thrombolysis with intracoronary or intravenous t-PA or with im t-PA by enhancement of absorption with hydroxylamine and electrical field stimulation. However, hydroxylamine induces transient haemodynamic effects and methaemoglobinaemia. In this study we characterised factors influencing im absorption of t-PA and the potential utility and toxicity of analogues of hydroxylamine (HA) in 109 rabbits. Absorption was measured after im injection of 1·5–13·0 mg/kg of rt-PA (50 mg/ml) in solution with HA (2·6–175 mg, n = 25), in hypertonic media (0·63 mol/l sodium chloride, n = 2), with vasodilators (0·01 mol/l adenosine or 0·09 mol/l hydralazine, n = 5), with analogues of HA (n = 72) or t-PA alone (n = 5). Methylamine was particularly effective, lacked the haemodynamic effects associated with HA, and was not associated with methaemoglobin production. Methylamine plus field stimulation elicited functionally active blood levels of t-Pa within 5 minutes of injection that were of similar magnitude to those achieved with HA (200 *vs* 361 ng/ml for 1·5 mg t-PA/kg, n = 12), with 20% blood activity remaining after 30 minutes. Only modest inflammation and interstitial haemorrhage were evident microscopically at the injection site after 48 hours. Vasodilators, hypertonic media, reduced amounts of HA or rt-PA alone led to much lower blood levels of rt-PA (14, 65, 46, 4 ng/ml/mg rt-PA respectively). Thus enhancement of absorption of t-PA with methylamine leads to dose dependent effective (fibrinolytic) blood levels of rt-PA after im injection (200 to 954 ng/ml) without the potentially deleterious effects associated with other absorption enhancing agents.

## Treatment of end stage heart failure by ultrafiltration

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Seven patients (6 male; age range 36–73 yr) in end stage heart failure were treated by ultrafiltration of venous blood through a polyacrylonitrile membrane (1·1 m$^2$; cutoff point MW 20 000). All patients were in class IV NYHA with primary congestive cardiomyopathy (2 cases) or ischaemic heart disease (5 cases); all had been treated with inotropic (I), diuretic (D), and vasodilator (V) agents in different combinations and had shown diminished response to drugs (despite increasing dosages), ingravescent oliguria, gain in body weight, and refractory oedema. One to five sessions of ultrafiltration were performed over a maximum of nine days with a body weight loss of 3·5 to 14·7 kg. Clinical improvement (respiratory distress and oedema) occurred rapidly; heart failure reappeared in one patient two weeks after ultrafiltration, and death followed in a few days; a second patient had a successful heart transplantation three weeks after ultrafiltration; in the remaining five treatment with I/D/V at moderate dosage was resumed after ultrafiltration and a pronounced clinical improvement (NYHA II/III) was maintained. One patient died a year later from stroke, and four are still alive 3, 6, 9, and 21 months after ultrafiltration treatment.

These data suggest that in end stage heart failure ultrafiltration may help in restoring the response to medical treatment and in improving clinical state in cases where heart transplantation is not immediately accessible or not indicated.

## Neuroendocrine mechanisms in acute myocardial infarction

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In acute myocardial infarction inappropriate or excessive neuroendocrine activation may have important physiological consequences; little is known about the relation between the magnitude of such stimulation and the extent of myocardial dysfunction. We investigated the extent of activation of the renin-angiotensin system in 36 consecutive patients after myocardial infarction. Left ventricular ejection fraction (LVEF) was assessed by gated radionuclide ventriculography within 6 hours of the onset of symptoms and plasma active renin and catecholamines were measured on admission and again on day 3. Mean renin concentration was 70·4 μU/ml (range 4–549) on admission with similar concentrations in uncomplicated cases (group 1, $n=25$) and in heart failure (group 2, $n=11$; 73·4 (23) *vs* 63 7 (22) (SEM)). LVEF was lower in group 2 (23 *vs* 35%; $p<0\cdot005$) in whom peak creatine kinase concentration were higher (3250 *vs* 2190 U/l; $p<0\cdot05$). Renin concentrations were within the normal range (10–50 μU/ml) in 23/36 patients on admission compared with only 6/36 on day 3. Mean renin rose to 251 (115) μU/ml but was significantly higher in group 2 than in group 1 (591 *vs* 103; $p<0\cdot05$). Catecholamine concentrations were raised on admission—adrenaline 1·7 (0·6) nmol/l (normal range, undetectable–0·2), noradrenaline 3·6 (0·95) nmol/l (normal range 0 8–3·0), with higher concentrations in group 2 than in group 1 (3·68 *vs* 0·51 ($p<0\cdot01$) and 6·35 *vs* 1·93 ($p<0\cdot02$) respectively). By day 3, although catecholamine concentrations had fallen, noradrenaline concentrations remained significantly higher in the patients with heart failure—4·83 *vs* 1·62 nmol/l; ($p<0\cdot001$). Thus significant activation of the renin-angiotensin and sympathetic nervous systems occurs in myocardial infarction, particularly in those with extensive infarcts leading to heart failure, but renin remains raised in many uncomplicated cases and this might not be wholly beneficial for tissue perfusion and myocardial function.

## Changes in nuclear magnetic resonance during the first two weeks after myocardial infarction in man

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The magnetic resonance parameter $t_1$ (spin lattice relaxation time) of myocardium increases after coronary occlusion of 30 min in dogs and increases further with occlusion of 2–3 hours. Changes are more pronounced if reperfusion is allowed. These changes correlate with myocardial water content. Our preliminary studies demonstrated increases in $t_1$ after myocardial infarction in man with values above 390 ms (normal 305 (25) ms). We now report $t_1$ changes during the 14 days after myocardial infarction, comparing patients with ($n=23$) and without ($n=11$) coronary reperfusion. Patients were imaged in a low field resistive imager (0·08 tesla) and $t_1$ maps were obtained for 16 mm transverse and coronal sections. For analysis the myocardium was divided into six standard regions of interest for each section. Thirty three of the 34 patients studied within two weeks of infarction had a $t_1$ value above 390 ms; at day 1–3 the maximum $t_1$ was 413 (29) ms ($n=23$) compared with 430 (41) ms ($n=22$) at day 4–7 and 436 (40) ms ($n=24$) at day 8–14. Four of the 23 patients studied at day 1–3 had normal $t_1$ values which subsequently became abnormal. The number of regions with an increased $t_1$ at each interval was 2·0 (1·5), 2·6 (2·4), and 2·8 (1·9) respectively. There was no significant difference between patients with or without reperfusion. The delayed increase in $t_1$ mirrors the reparative process and events other than oedema must also influence this relaxation parameter.

## Placebo controlled investigation of anisoylated plasminogen streptokinase activator complex (APSAC) for thrombolysis in acute myocardial infarction

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Anisoylated plasminogen streptokinase activator complex (APSAC) is a new agent designed to produce thrombolysis without a major effect on systemic coagulation variables. This report describes the first placebo controlled double blind reperfusion study of APSAC in acute myocardial infarction. Unequivocal documentation of reperfusion was provided by coronary angiography before and after the drug intervention. Twenty patients with acute transmural infarction underwent coronary angiography 3·0 (1·1 hours after the onset of symptoms. This demonstrated total occlusion of the infarct vessel in 16 cases. The patients were then randomised to intravenous APSAC 30 mg ($n=9$, group A) or placebo ($n=7$, group B) 3·2 (1·1) hours after the onset of symptoms. Repeat angiography 90 minutes later demonstrated reperfusion in six of group A but in none of group B ($p<0{\cdot}05$). Reperfusion was associated with an early peak in serum creatine kinase (9·6 (3·9) *vs* 21·7 (4·7) hours) ($p<0{\cdot}05$). Full cardiac catheterisation was undertaken at three days to guide subsequent management. Persistent luminal patency was present in all but one of the six patients with early reperfusion and three additional patients showed late reperfusion (two group A, one group B). No haemorrhagic complications occurred during the study. One patient from group B died in intractable heart failure. These preliminary data confirm the thrombolytic efficacy of APSAC in acute myocardial infarction and indicate that the drug may be used safely by the intravenous route with a 66% early reperfusion rate.

## Analysis of electrocardiographic changes occurring during thrombolytic therapy for acute myocardial infarction

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Electrocardiograms from 100 patients on thrombolytic treatment for coronary thrombosis were reviewed. Two groups were identified—52 patients (52%) showed abrupt reduction 60–120 minutes after treatment in both ST segment ($p<0{\cdot}01$) and T wave height ($p<0{\cdot}01$) with resolution of reciprocal changes. These changes did not occur in the remaining 48 patients (48%). Atrial fibrillation, ventricular extrasystoles, tachycardia, and fibrillation were evenly distributed throughout the two groups. Idioventricular rhythm occurred in 16 patients; 13 of these patients had simultaneous ST and T wave changes. At arteriography open infarct related arteries were found in 47 patients (94%) in the group with clear electrocardiographic changes and in 29 (60·4%) of those with no change. Open arteries were also present in 14 of 15 patients (93%) showing idioventricular rhythm. Two patients were excluded from analysis because of obvious clinical reocclusion. A trend in ejection fraction was seen; values were highest in patients with clear electrocardiogram change (46·9%) and lowest in those with occluded arteries (42·2%).

After thrombolysis for infarction 52% of patients show clear abrupt change in ST elevation and T wave height. These changes were 79% specific and 63·5% sensitive for coronary re-opening as judged by angiography. Idioventricular rhythm was a frequent and highly specific (96%) indicator of coronary re-opening; however, it was relatively insensitive (22%). A trend towards improved left ventricular function was seen in patients with clear abupt electrocardiogram changes. Careful scrutiny of routine 12 lead electrocardiograms provides useful and accurate information relating to myocardial reperfusion after thrombolytic treatment.

## Changes in left ventricular regional asynchrony after intracoronary thrombolysis

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To study changes in asynchronous left ventricular wall motion after intracoronary thrombolysis, ventriculograms were obtained before and 4·3 (2·5) weeks after lysis in 23 patients treated within 3·5 (3·1) hours of the onset of pain. Lysis was achieved in 19, and patency was maintained at restudy in 16. Angiograms were digitised frame by frame, LV volumes, ejection fraction, and peak ejection rate were unchanged, and peak filling rate fell whether or not the artery was patent. Regional wall motion was studied by means of isometric and contour plots. The affected area showed simple hypokinesis in 10 patients, which was unchanged at restudy in nine and improved in one. Delayed inward motion during isovolumic relaxation was present in 14 cases, with or without additional hypokinesis; it improved in eight and returned to normal in six—more often than it did in simple hypokinesis ($p<0{\cdot}02$). Dyskinesis (three cases) and hyperkinesis (five cases) resolved in all. Outward motion during isovolumic relaxation reverted to normal in four of five cases, and outward motion reverted to normal during isovolumic contraction in five of seven. Improvement was more frequent when the affected artery was uncompromised by residual stenosis ($p<0{\cdot}01$). Arterial flow was re-established and maintained more often when the affected area showed asynchrony rather than simple hypokinesis ($p<0{\cdot}025$). Conclusions: (1) Asynchronous motion is the commonest regional abnormality early after coronary artery thrombosis. (2) Its increased frequency of recovery confirms that it represents residual contractile activity. (3) Its presence increases the chance of flow being re-established with lysis in the affected coronary artery.

## Trial of early nifedipine treatment in patients with suspected myocardial infarction (the TRENT study)

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Approximately 9000 consecutive patients admitted with suspected myocardial infarction to coronary care units (CCU) in nine hospitals were considered for admission to a randomised double blind study designed to compare the effect on mortality of nifedipine 10 mg four times a day with that of placebo treatment. 4700 patients were excluded but were nevertheless followed and their overall fatality rate at one month was 18%. 4488 patients were randomly allocated to nifedipine or placebo treatment which started immediately after assessment in the CCU, and the groups proved to be well matched. 64% of patients in both treatment groups sustained an acute myocardial infarction. 595 (26%) of the 2238 patients allocated to nifedipine treatment were withdrawn from the study as were 562 (25%) of the 2250 patients allocated to placebo treatment. All the patients were followed for one month, the duration of the study period. 150 (6·7%) of the patients initially allocated to nifedipine treatment died in the first month, compared with 141 (6·2%) of those initially allocated to placebo. The one month infarct mortality rates were 10·2% and 9·2% respectively. By "intention to treat" analysis there was thus an increase in overall mortality of 8% in the nifedipine group (95% confidence intervals +30% to −14%). Although this result embraces a small potential benefit from nifedipine treatment the trial was discontinued on the advice of the ethical committee who considered that it was unlikely that a statistically confident beneficial effect would be demonstrated if the trial were continued. Analysis of the subgroups formed when the results were available did not suggest that any group of patients with suspected myocardial infarction might benefit from early nifedipine treatment.

## Impaired right ventricular function following transvenous fulguration of atrioventricular conduction

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After transvenous fulguration of atrioventricular (AV) conduction, 13 of 22 patients who had had no evidence of structural heart disease before the procedure complained of exertional dyspnoea. Patients were aged 19–63, 17 were female, and 16 had had AV re-entrant tachycardia. Resting right and left ventricular ejection fractions (RVEF and LVEF) were blindly measured by radionuclide angiography 10–42 months after fulguration. RVEF was significantly lower in patients who complained of exertional dyspnoea (33·8 (8·4)%, mean (SD), range 21–48%) than those who remained free of dyspnoea (40·5 (4·1%), range 37–48%, $p<0·05$) and also compared with a control group of eight subjects with no cardiorespiratory disease (41·9 (7·0)%, $p<0·05$). There was no difference in LVEF between patients who complained of dyspnoea (52·5 (13·8)%) and those who did not (52·6 (5·0)%). Similarly, there was no difference in the number of shocks (1·9 (0·9) and 2·1 (0·6)) or total energy delivered (658 (291) J and 711 (198) J respectively) between the two groups. Exercise capacity (Bruce protocol) as a percentage of predicted normal value was significantly lower in patients who complained of dyspnoea (51 (24)% *vs* 81 (13%), $p<0·01$). We conclude that right ventricular function may be impaired in some patients after tranvenous fulguration of AV conduction and that this may contribute to their reduced exercise capacity and exertional dyspnoea.

## Three deaths after attempted high energy catheter ablation of ventricular tachycardia

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Catheter ablation of ventricular tachycardia (VT) may abolish VT without the need for drugs or operation. However, the extent of the damage produced is unpredictable. Three cases of VT that illustrate potential problems of this treatment are described. All these patients were refractory to antiarrhythmic drugs and two were not suitable for surgical resection because of poor left ventricular (LV) function resulting from myocardial infarction (MI). The first patient had right ventricular (RV) dysplasia and VT originating from the RV outflow tract that was provoked only by strenuous exercise. After two attempts at catheter ablation with up to 400 J, the VT on exercise was reduced to four beats. Two weeks later he suddenly became dyspnoeic and dizzy on mild exertion and died. The second patient had an LV aneurysm and incessant VT originating from the apical septum with earliest activation on the RV aspect. A transseptal shock of 200 J was unsuccessful so 360 J was delivered to the RV apical septum. The patient collapsed within minutes of this procedure. Cardiac tamponade was confirmed at necropsy without any discernible damage to the fibrotic LV septum. The third patient developed incessant fascicular tachycardia after a second MI. On four occasions, multiple DC shocks of up to 360 J were delivered both to the region of the posterior fascicle and the His bundle. Although it was initially suppressed, fascicular tachycardia returned and, after the last procedure, it was accompanied by paroxysmal ventricular flutter. Despite combination drug treatment the patient died suddenly two months later. Catheter ablation should be avoided at the RV apex, it may be ineffective on fibrotic endocardium, and can provoke malignant ventricular arrhythmias. It should be reserved for patients in whom other treatment is either ineffective or unsuitable.

## Assessment of the haemodynamic consequences of varying pacemaker modality by Doppler ultrasound

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Doppler ultrasound was used to assess the haemodynamic consequences of varying pacing modalities in 10 patients during electrophysiological study. Cardiac output estimation, by a previously validated Doppler method, was made during atrial, ventricular, and atrioventricular sequential pacing at cycle lengths of 400 ms up to 800 ms. Atrioventricular intervals for sequential pacing ranged from 50 ms to 250 ms. Examination was performed with a Vingmed Alfred Doppler velocimeter with spectrum analysis and separate cross sectional echocardiographic imaging. Cardiac outputs were significantly lower during ventricular pacing (4·1 (1·5) l/min) compared with either atrial (5·1 (1·5) l/min, $p<0{\cdot}005$) or optimal atrioventricular sequential pacing (5·4 (1·6) l/min, $p<0{\cdot}001$). Varying the atrioventricular interval produced changes in cardiac output at each cycle length; these were more pronounced at shorter cycle lengths (mean change 12% at 700 ms and 21·5% at 400 ms, $p<0{\cdot}001$). The atrioventricular interval giving optimal cardiac output was unpredictable, varying with cycle length and between individuals. In conclusion, Doppler ultrasound can provide a simple non-invasive method of determining the haemodynamic consequences of intracardiac pacing, with the potential to predict the optimal pacing modality in individual patients before permanent pacemaker insertion.

## Haemodynamic assessment of dual chamber pacing in hypertrophic cardiomyopathy using radionuclide ventriculography

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To assess the mechanism of haemodynamic improvement in patients with hypertrophic cardiomyopathy in whom DDD pacemakers had been implanted because of failure of conventional medical treatment, six patients (mean age 47 years, range 22–48) were studied by gated radionuclide ventriculography in different modes of pacing. The patients were imaged in sinus rhythm (SR), VVI, and DDD modes with a three minute interval between each study. Measurements made were ejection fraction (EF), time to peak filling rate (TPFR), time to peak ejection rate (TPER), and percentage of stroke volume ejected during the first third of systole. Results showed no difference in EF between pacing modes. The TPFR was 574 (54) ms (mean (SD)) in SR, 571 (37) ms in VVI mode, and 524 (22) ms in DDD mode. The TPER was 169 (22) ms in SR, 209 (67) ms in VVI mode, and 193 (31) ms in DDD mode. The percentage of the stroke volume ejected during the first third of systole was 55 in SR, 40 in VVI mode, and 45 in DDD.

It is concluded that radionuclide ventriculography is a useful non-invasive method for following the progress of these patients; normalisation of left ventricular filling and ejection occurs with DDD pacing in hypertrophic cardiomyopathy; the mechanism of improvement is probably asynchronous left ventricular contraction with appropriately timed atrial synchrony.

## An intra-patient comparison of ambulatory blood pressure during chronic DDD and VVI pacing

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Fifteen patients (age 54–81 years) with programmable dual chamber pacemakers (Cordis 233F or Biotronik Diplos 05) were randomly allocated single blind to DDD or VVI pacing. After an equilibration period of at least four weeks each patient underwent an assessment of symptoms by visual analogue scales and a 24 hour intra-arterial ambulatory blood pressure recording. The pacemaker was then programmed to the opposite mode and the observations were repeated after another period of at least four weeks. 12 of the 15 patients expressed a strong symptomatic preference for DDD pacing; patients also reported significantly more dyspnoea, fatigue, and dizziness during VVI pacing (in each case $p \leqslant 0{\cdot}05$, Wilcoxon rank sign test). Computer aided beat by beat analysis showed that blood pressure was significantly lower and significantly more variable during VVI pacing. The mean (SEM) daytime systolic blood pressure was 139·3 (3·8) mm Hg during DDD pacing compared with 131·3 (4·5) mm Hg during VVI pacing ($p < 0{\cdot}05$, paired $t$ test). The median (range) standard deviation of daytime systolic blood pressure, an index of blood pressure variability, was 18·5 (15–28) mm Hg during DDD pacing and 24 (14–31) mm Hg during VVI pacing ($p < 0{\cdot}005$, Wilcoxon rank sign test). Hence, transient episodes of hypotension were more common during VVI pacing, which may partly explain why the patients in general felt better during DDD pacing.

## Activity sensing rate responsive permanent cardiac pacing in very young children

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Single chamber ventricular pacemakers which can vary the pacing rate according to sensed physical activity should be especially advantageous in very young children in whom dual chamber physiological pacing is often technically difficult to achieve. Five young children mean age 5·8 years (range 3·3–11) and a two week old infant have received small single chamber activity sensing rate responsive pacemakers (Medtronics Activitrax). The indication for pacing was complete heart block in all cases (four had associated structural heart disease). Pacemakers were implanted in the abdomen in five children and in the pre-pectoral region in one. Five patients had endocardial electrodes (including the neonate) and one child had an epicardial lead. In five children effort capacity could be determined by treadmill exercise tests (Bruce protocol). Duration of exercise was prolonged by an average of 1·7 (0·1) minutes (SEM) in the rate responsive mode compared with fixed rate demand pacing (VVI) between 70 and 90 beats/min, the standby VVI rate being predetermined by programming and using the spontaneous atrial rate as a guide. In the two week old baby the pacemaker was programmed to give maximum heart rate response with the lowest activity threshold. Holter monitoring showed an average ventricular rate of 110 beats/min with a maximum of 140 beats/min. We conclude that even in very small children rate variable pacing in response to physical activity is feasible and permits more physiological heart rate responses.

## The effect of right and left ventricular function on early and late mortality following surgical repair of post-infarction ventricular septal defect

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Preoperative investigations of 60 patients (aged 46–73) who underwent repair of post-infarction ventricular septal defect (VSD) were reviewed to assess the effect of right and left ventricular function on early (< 30 days) and late mortality. Left ventricular ejection fraction (LVEF) was calculated from right anterior oblique ventriculograms; right ventricular (RV) function was assessed by measuring per cent reduction in RV mid-cavity diameter from left anterior oblique ventriculograms. There were 23 early deaths and these patients had a significantly lower per cent reduction in RV mid-cavity diameter (16·5 (9·5)%, mean (SD)) than the 37 survivors (26·7 (10·6)%, $p < 0{\cdot}01$). There was no difference in LVEF (33·8 (10·2)% and 31·7 (9·7)% respectively) between the two groups. The 37 survivors have been followed up for 2–108 (mean 38) months and there have been 14 late deaths. There was not difference in per cent reduction in RV mid-cavity diameter between those who died (26·0 (12·2)%) and those who survived (27·1 (9·8)%), but LVEF was significantly higher in the survivors (26·2 (9·3)% *vs* 35·0 (8·5)%, $p<0\cdot01$). Early mortality was associated with inferior rather than anterior infarction ($p<0\cdot01$), but the late result was not related to infarct site. We conclude that after surgical repair of post-infarction VSD, site of infarction and right ventricular function are major determinants of early mortality, whereas left ventricular function is more important in determining the long term prognosis.

## Ventricular function following heterotopic cardiac transplantation

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Ventricular function has been studied in 16 patients one year after heterotopic cardiac transplantation and in 11 of these after a second year. This group is taken from 26 patients undergoing heterotopic cardiac transplantation from January 1983. Five died early and five have not reached the first anniversary. Heterotopic cardiac transplantation was combined with aneurysmectomy in 11 and with coronary artery bypass graft in 12. One underwent donor excision for rejection after one year. All survivors have good exercise tolerance achieving 9·7 (3·1) min and 8·7 (3·2) min of the Bruce exercise protocol at one and two years. Diastolic pressures were lower in the donor heart with left ventricular end diastolic pressure being 11·7 (6·1) mm Hg in the donor and 14·2 (4·9) mm Hg in the recipient. Mean pulmonary capillary wedge pressure was 12·4 (4·6) mm Hg and mean mitral valve gradient was higher for the donor hearts. Systolic function was better in the donor heart with higher peak systolic pressure (143 (17·6) mm Hg) than the recipient (120 (26·6) mm Hg) and a faster rise of pressure. Peak systolic pressure was frequently augmented when the ventricles contracted together. Left ventricular angiography showed very good donor function in 14 at one year and nine at two years. Five patients with aneurysm resection showed good ejection from recipient ventricle to aorta, all with ejection fraction over 30%. One other had good ejection and four modest ejection from the recipient ventricle. Clot was present in seven recipient ventricles. Cardiac performance after heterotopic cardiac transplantation remains good for two years and a proportion retain significant recipient function.

## Medial and endothelial damage can be avoided during surgical preparation of autologous saphenous vein coronary bypass grafts

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Damage to saphenous vein media and endothelium during surgical preparation may promote subsequent coronary vein graft occlusion. ATP concentration and ATP:ADP ratio were measured to assess medial function and stimulated (vortex mixing) prostacyclin production to assess endothelial function. Freshly isolated vein had 450 (20) nmol/ATP/g, an ATP:ADP ratio of 2·4 (0·1) ($n=38$), and produced prostacyclin at 13 (1) nmol/g ($n=52$). Vein subjected to conventional surgical preparation (dissection, adventitial stripping, side branch ligation, distension at <300 mm Hg and peroperative storage in patient's heparinised arterial blood at 23°C, distal anastomosis following cardioplegic arrest, and subsequent proximal anastomosis) had an ATP concentration of 260 (40) nmol/g, an ATP:ADP ratio of 1·3 (0·1) ($n=16$), and produced prostacyclin at 6·3 (0·9) ng/min per g ($n=14$) ($p<0\cdot001$ *vs* freshly isolated vein for all three variables). Vein subjected to a modified procedure (side branch ligation followed by anastomosis to the ascending aorta using an exclusion clamp, distension at arterial pressure after temporary removal of the clamp, and distal anastomosis during subsequent cardiopulmonary bypass/cardioplegic arrest) had an ATP concentration of 480 (80) nmol/g, an ATP:ADP ratio of 2·5 (0·1) ($n=8$), and produced prostacyclin at 12 (2) nmol/min g ($n=11$) (NS *vs* freshly isolated vein, $p<0\cdot001$ *vs* conventional preparation for all three variables).

Thus conventional surgical preparation damages both the venous media and endothelium. Damage can be avoided, however, with the modified procedure. The impact of improved intraoperative preservation on graft patency may now be tested.

## Ten years' clinical experience with the pericardial xenograft

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Since 1975, 1018 pericardial valves have been implanted in 741 patients. Single valve replacement was undertaken in 224 patients with aortic (AV), 302 patients with mitral (MV), five patients with tricuspid valve disease, and 190 patients had multiple valve (DV) replacement. Of the total number of valves used 578 were standard and 440 low profile Ionescu-Shiley pericardial xenografts. Hospital mortality was 6·3%. The 714 hospital survivors were followed up for 3 to 111 (mean 51·9) months. Long term anticoagulants were not used. The predicted actuarial survival rates are 85·8 (8·7)% for AV, 84·1 (7·8)% for MV, and 80·2 (10·3)% for DV 10 years after operation. Valve thrombosis was not observed. The actuarial freedom from embolism was 96·4 (2·7)% for AV, 96·8 (2·3)% for MV, and 97·2 (2·0)% for DV at 10 years after valve replacement; the linearised incidence being 0·55 episodes per cent per annum for AV, 0·62 for DV, and 0·55 for MV. Twenty five pericardial xenografts were replaced because of dysfunction (valve abrasion and calcification were responsible for 16 and 8 valve failures respectively). The linearised incidence of valve dysfunction was 0·77 episodes per cent per annum; the actuarial predicted freedom from valve dysfunction being 83·0 (9·1)% for AV, 89·3 (7·0)% for MV, and 82·4 (11·0)% for DV 10 years after operation. The valve durability was 87·8 (4·9)% for standard pericardial xenografts at 10 years and 99·4 (0·6)% for low profile pericardial xenografts at 5 years after valve replacement.

These clinical experiences confirm the long term durability of the standard pericardial xenograft and the in vitro superiority of the low profile pericardial xenograft.

## Can left ventricular ejection fraction by cine computed tomography be determined by a single slice?

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Cine computed tomography is a new cardiac imaging technique. Non-gated images can be obtained at 17 frames/second. 27 patients were divided into two groups. Group 1 (10 females, 5 males, age 35–74) underwent cine CT in the transaxial view (no rotation no tilt). Group 2 (3 females, 9 males, age 46–70) had cine CT in the long axis view (20°C counterclockwise angulation, no tilt). Contrast was injected via an antecubital vein and timed for maximal opacification of the ventricles. The left ventricle (LV) was imaged in the movie mode in contiguous slices of 8 mm thickness. End systolic and end diastolic frames were identified for each slice. LV cavity areas were determined by two methods ($M_1$ or $M_2$) of edge detection ($M_1$ = unassisted visual; $M_2$ = setting of the Hounsfield level at half the difference between the contrast in the cavity and the myocardium with the window width at one). LVEF was measured by summation of end diastolic (EDV) and end systolic (ESV) values for each slice and by selecting the largest central slice by volume for ESV and EDV. LVEF as an average of two sinus beats was measured in all patients by right anterior oblique single plane contrast ventriculography at catheterisation using the area-length method. In group 1 there was poor correlation between catheter EF and cine/CT midslice EF ($M_1$, $r = 0·69$, $M_2$, $r = 0·76$) and total volume EF ($M_1$, $r = 0·77$; $M_2$, $r = 0·81$). For group 2 there was good correlation between catheter EF and cine/CT midslice EF ($M_1$, $r = 0·96$; $M_2$, $r = 0·93$) and total volume EF ($M_1$, $r = 0·96$; $M_2$, $r = 0·93$). It is concluded that the view used affects the accuracy of the examination, that edge detection plays a less important role than cardiac orientation, and that a single slice in the long axis view can be used to calculate ejection fraction.

## The clinical value of a new myocardial imaging agent—technetium-99m tertiary butyl isonitrile (Tc-99m BIN)

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Technetium-99m is less expensive and has a more favourable energy emission for scanning with a gamma camera than thallium-201. A new myocardial imaging agent, Tc-99m BIN, was studied in 50 subjects. There were five normal controls, 15 patients with myocardial infarction (MI), and 30 with angina due to angiographically documented coronary artery disease (CAD). After the intravenous injection of between 3 to 5 mCi of Tc-99m BIN, subjects were scanned by means of a gamma camera with a converging collimator. In normal subjects the myocardium was clearly seen at 60 minutes at rest and at 30 minutes when the subject was first exercised. Patients with MI were scanned at rest and defects in myocardial uptake were clearly shown. Each patient with angina received thallium-201 and Tc-99m BIN separately after maximal treadmill exercise. Optimal images with Tc-99m BIN were obtained at 30 minutes after exercise and at four hours for redistribution scans. Reversible perfusion defects were seen and the images with Tc-99m BIN were superior to those obtained with thallium-201 in the same patients.

These studies suggest that Tc-99m BIN is a good myocardial scanning agent that may be superior to thallium-201.

## An objective non-invasive method for detecting early diastolic dysfunction in patients with coronary artery disease

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The demonstration of abnormal left ventricular (LV) diastolic function in ischaemic heart disease (IHD) has led to renewed interest in methods of assessing LV function non-invasively. An automated method for assessing LV diastolic function from equilibrium radionuclide angiography with Tc-99m has been developed. This technique was used to study 30 normal subjects and 39 patients with IHD. ECG gating was used to collect the data in 32 frames per cardiac cycle with 5% gate tolerance. A second derivative method of edge detection was used to define the LV in all frames. A high resolution time-activity curve was then obtained from which a first derivative sample was generated to identify points of peak filling and emptying. Peak filling rate (PFR, EDV/s), time to peak filling rate (TPFR, ms), filling fraction (FF), and early filling rate (EFR) (EDV/s) were calculated. The mean (SEM) normal values were: PFR 3 1 (0 07), TPFR 168 (8), FF 0·52 (0 03), EFR 1·5 (0·7). These were all significantly different in the patients: PFR 2·0 (0·08), TPFR 197 (9), FF 0·31 (0·2), EFR 1·0 (0·06) ($p<0\cdot001$, $p<0\cdot05$, $p<0\cdot001$, and $p<0\cdot001$ respectively). This study confirms that diastolic function is abnormal in IHD and that this may be detected before systolic dysfunction becomes apparent. This automated technique may be used to give a reliable objective assessment of diastolic function and to follow patient response to therapeutic interventions.

## A new non-invasive method of estimating left ventricular end diastolic pressure using pulsed Doppler ultrasound

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Left ventricular end diastolic pressure (LVEDP) is generally regarded as a useful indicator of left ventricular function. Its measurement has previously relied on invasive techniques. A new non-invasive method of estimating LVEDP is described. We have compared the ratio of the passive and active components of mitral flow with LVEDP measured at cardiac catheterisation in 20 patients (14 males, mean age 51·9 years, range 36–62) with ischaemic heart disease. None had valve disease and all were in sinus rhythm. Pulsed Doppler measurement of mitral flow were performed using the apical view to position the sample volume in the mitral orifice, with simultaneous ECG and LVEDP recordings. Each spectrally analysed mitral flow trace showed two diastolic peaks. The first represented passive flow from left atrium to ventricle and the second represented active flow due to atrial contraction. The mean of 10 consecutive recordings of the ratio of the areas of the two wave forms was calculated for each patient and found to correlate with LVEDP ($r=0\cdot78$ $p<0\cdot001$). Active mitral flow was lower with higher LVEDP. Mitral flow ratios of >2 were always associated with LVEDP >20 mm Hg. Reproducibility of the mitral flow ratio was assessed by making 10 separate measurements on the same individual within one hour; the correlation coefficient was 7·2%.

In conclusion, this technique offers a non-invasive and reproducible method of assessing LVEDP.

## Single vessel angioplasty in multiple vessel disease

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To assess the safety and efficacy of single vessel angioplasty in multiple vessel disease (MVD), a retrospective assessment was made of the results in 115 patients who were treated by single vessel angioplasty before the introduction of multiple vessel angioplasty. According to the Coronary Artery Surgery Study criteria 90 patients (68 male and 22 female) had single vessel disease (SVD) and 25 patients (22 male and three female) had MVD with one artery suitable for mechanical treatment. Other diseased arteries were unsuitable for surgery because of inaccessibility or calibre (nine patients), diffuse disease (seven patients), or total occlusion with Q wave infarction in the dependent territory (nine patients). The vessels treated in patients with SVD were the left anterior descending (77), right coronary artery (9), and left circumflex (4); and in patients with MVD they were the left anterior descending (15), right coronary artery (7), and left circumflex (3). Short and long term follow up was conducted. Technical success was achieved in 71 of 90 patients with SVD and in 19 of 25 with MVD. Emergency bypass grafting was necessary in six patients with SVD and in one with MVD. One patient with MVD died within 24 h of angioplasty. Angina was totally abolished in 67 and improved in three of the 71 SVD patients with successful angioplasty and was abolished in 13 and improved in four of 19 MVD patients who had successful angioplasty. In this small group of patients with MVD who had only one artery suitable for mechanical treatment, angioplasty was acceptably safe and improved symptoms. Thus single vessel angioplasty may have a place in the treatment of patients with multiple vessel coronary artery disease.

## Evolution of myocardial ischaemia during percutaneous transluminal coronary angioplasty

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Balloon inflation during coronary angioplasty is a useful model of acute coronary occlusion and regional myocardial ischaemia. The prevalence and duration of ischaemia during successive 60 second balloon inflations were assessed in 16 patients (11 with left anterior descending artery and five with right coronary artery lesions) by continuous six lead ECG and cross sectional echocardiography recording. ST segment elevation developed in 14 of the patients within 18 (12) (SD) seconds of balloon inflation and returned to baseline within 20 (9) seconds of deflation. Wall motion abnormalities on the echocardiogram were seen in all patients 15 (5) seconds after balloon inflation and had disappeared 13 (3) seconds after deflation. Time to onset of ischaemia as determined by both methods remained remarkably constant during successive balloon inflations. The rate pressure product (RPP) before balloon inflation correlated inversely with time to onset of ischaemia detected by both techniques: $r=-0\ 72$, $p<0\ 05$ (ECG); $r=-0{\cdot}67$, $p<0{\cdot}05$ (echocardiography). Nevertheless, evidence of ischaemia developed within 30 seconds in all patients regardless of RPP. This investigation of regional ischaemia during percutaneous transluminal coronary angioplasty indicates that ECG and echocardiography have a similar sensitivity for detection of acute ischaemia; resting myocardial oxygen consumption as reflected by RPP is an important determinant of the time to onset of ischaemia; manipulation of RPP alone is unlikely to have an important protective effect during percutaneous transluminal coronary angioplasty.

## Percutaneous laser thermal angioplasty

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The potential of laser energy in percutaneous angioplasty will not be realised until an intraluminal channel can be produced and vessel wall perforation can be reliably avoided. A metal tipped laser fibre (laser probe) with up to 10 W argon laser power was used for five to 60 s in 46 limbs in 44 patients undergoing percutaneous femoral/popliteal angioplasty. All 14 stenoses were successfully traversed. Of 32 occlusions (length 1 to 35 cm, mean 8 cm) 22 were initially probed at their proximal limits by a guide wire so that they could be classified as being potentially easy or difficult to cross by conventional means. Ten occlusions were classified as "impossible" because either previous attempts on angioplasty had failed or because they were anatomically unsuitable for conventional techniques. The probe successfully traversed all 10 easy, 11 of 12 difficult, and seven of 10 impossible occlusions. In one case mechanical wall entry with extravasation occurred (before laser energy was used) (this was probably due to a false passage produced by previous guide wire); there were no sequelae. In all the lesions that were successfully crossed an adequate initial channel (mean lumen diameter (MLD) 1·41 mm (0·27) (SD)) was produced for subsequent balloon dilatation (MLD 2·84 mm (0·88)).

Thus the laser probe facilitates angioplasty by providing an initial channel through lesions before balloon dilatation. It can traverse occlusions that are difficult or impossible to cross by conventional means and therefore has potential for increasing the role of angioplasty in the treatment of arterial disease.

## Percutaneous transluminal valvotomy for rheumatic mitral stenosis using a double balloon technique

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Severe mitral stenosis currently requires surgical intervention. The feasibility of mitral balloon valvotomy (that is commissural splitting) was demonstrated during cardiac surgery. A transatrial double balloon technique was then used to perform percutaneous mitral valvotomy in nine patients with rheumatic mitral stenosis. Nine symptomatic patients (23 (6) years mean (SD) with severe non-calcific mitral stenosis who were in sinus rhythm were selected. The study protocol included left and right cardiac catheterisation, calculation of the mitral valve area by the Gorlin formula, and left atrial and left ventricular angiograms before and immediately after balloon dilatation. The left atrium was entered with two number 12 French Mullins transseptal sheaths from both femoral veins. Two pre-shaped 0·038 inch guide wires were positioned in the left ventricle, and two Medi-tech balloons (12 to 15 mm in diameter) were advanced across the mitral valve and simultaneously inflated up to 5 atmospheres. In seven patients, the mitral valve area increased from 0·71 (0·19) to 2·0 (0·8) $cm^2$, and the mean mitral gradient decreased from 15 (3·5) to 2 6 (2 7) mm Hg. The procedure was unsuccessful in the first two cases, in which small balloons (12 mm) were used. During inflation, systolic aortic pressure was maintained above 45 mm Hg. Three patients had trivial mitral incompetence after successful dilatation; otherwise there were no complications. No left to right shunt at the atrial level was detected by oximetry.

It is concluded that in selected patients severe rheumatic mitral stenosis can be successfully relieved by a percutaneous double balloon technique without complications.

## Somatostatin: a neuroregulatory peptide with electrophysiological activity

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The peptide somatostatin, which acts in part as an automatic neurotransmitter, is present in human cardiac tissue, with high concentrations in the sinus and atrioventricular (AV) nodes. To assess the possible physiological and pharmacological roles of somatostatin in the heart, its electrophysiological effects were compared with those of the calcium antagonist verapamil in 10 patients undergoing investigation of AV re-entry tachycardia (accessory AV pathway 4; dual intranodal pathways, 6). During sinus rhythm, somatostatin (12·5 μg/min for 10 min) prolonged cycle length by 45 (37) ms (mean(SEM)) whereas verapamil shortened it by 30 (21) ms ($p < 0·01$). Somatostatin had a less pronounced effect than verapamil on AV nodal conduction as judged by prolongation of both AH interval (11 (3) *vs* 43 (8) ms, $p < 0·005$) and AV nodal effective refractory period (39 (8) *vs* 94 (38) ms, NS). Both drugs terminated tachycardia in 6/7 patients; verapamil after 35 (3)s by AV conduction block. With somatostatin, termination occurred later (after 277 (90) s); in 5/6 by invasion of the re-entry circuit by ventricular extrasystoles. Prolongation of tachycardia cycle length before termination was more pronounced with verapamil than with somatostatin (94 (19) *vs* 29 (11) ms, $p < 0·05$). The electrophysiological properties as well as the anatomical distribution of somatostatin suggest that it may participate in the mediation of autonomic control of the sinus and AV nodes.

## The misdiagnosis of ventricular tachycardia—results of a postal survey

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Ventricular tachycardia may be misdiagnosed, and this can lead to serious consequences. A postal survey was carried out to examine the diagnostic accuracy of clinicians faced with this arrhythmia. Copies of referral ECGs from six patients with ventricular tachycardia who had been misdiagnosed as having supraventricular tachycardia were sent to a random selection of physicians. Each 12 lead ECG had ample data by classic criteria for the correct diagnosis to be made, and each patient also had an electrophysiological study performed to optimise treatment and to confirm the diagnosis. The ECGs all showed a regular rhythm, and the rates ranged from 176 to 200 beats/min. Five had a QRS width ≥150 ms, five had a QRS axis ≥60°C, five had atrioventricular dissociation, one had fusion beats, one had concordance across the chest leads, and three had morphological features that excluded bundle branch aberration.

There were 200 replies, 148 from consultants, 49 from those in training, and three from others. Fifty eight were cardiologists, 90 had a major cardiac interest, and 52 had other specialist interests. Twenty two were aged ≤30, 79 were 31–40, 51 were 41–50, and 48 were ≥51 years. The diagnosis was correct in 558 (47%) of cases (ranging from 30–79% between ECGs). Twelve (6%) respondents had no correct answers, 46 (23%) had one, 41 (21%) had two, 38 (19%) had three, 21 (10%) had four, 20 (10%) had five, and only 22 (11%) had all replies correct. Forty two physicians (21%) had five or six correct answers including 20% of consultants and 27% of those training. This was also the result for 34% of the cardiologists, 22% of those with a major cardiac interest, and 4% of the others; and 26% of those aged 31–50 and 11% of the others.

Misdiagnosis of ventricular tachycardia was common despite characteristic ECGs and was made even by experienced cardiologists.

## Drug related arrhythmia induction during electrophysiological testing

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Electrophysiological testing (EPS) has been suggested as a means of identifying the arrhythmogenic potential of antiarrhythmic drugs. The incidence of arrhythmia induction (AI) was determined in 314 patients with inducible ventricular arrhythmias undergoing 801 individual drug studies. The definitions of AI that were used and their incidence were (*a*) conversion of non-sustained ventricular tachycardia (VT) to a sustained arrhythmia (18%); (*b*) conversion of stable sustained VT to a sustained arrhythmia requiring cardioversion (7%); (*c*) reduction in aggressiveness of stimulation mode (20%); and (*d*) development of spontaneous sustained VT (0·5%). The drug regimens included 15 single agents and eight combinations. The incidence of AI ranged from 15% to 37% (mean 23%) for single agents and from 22 to 30% (mean 29%) for combination regimens. Quinidine with the lowest incidence caused significantly less AI than amiodarone, flecainide, indecainide, quinidine plus mexiletine, and amiodarone plus procainamide ($p<0·05$). No combination regimen caused significantly more AI than any other combination. In 40 studies of combination regimens, one component of which had previously produced AI, 22 (55%) did not manifest AI. Drug concentrations for single agents were all within the therapeutic range. In conclusion, drug-related AI is common during EPS and the development of AI while the patient is on a single agent does not preclude its use in combination regimens.

## Indirect evidence for participation of His Purkinje system in ventricular activation during ventricular tachycardia

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Currently there is not enough evidence to determine whether the His Purkinje system (HPS) participates in myocardial activation during ventricular tachycardia (VT). To test whether the HPS was engaged in ventricular activation during ventricular tachycardia the following were analysed (*a*) the effect during sinus rhythm of HPS conduction delay manifested as bundle branch block and (*b*) the effect of HPS conduction time (H-V interval) on the QRS duration of VT in 125 patients with sustained tachycardia. During sinus rhythm 67 patients had a narrow QRS complex and they all had normal H-V interval (mean 45·7 (5) ms), 34 patients had right bundle branch block with mean H-V interval of 49 (7) ms (NS compared with the former patients), and the remaining 24 patients had left bundle branch block and corresponding H-V interval of 63 (9) ms ($p<0·05$ compared with those with narrow QRS). During VT, QRS duration of patients with narrow QRS ranged from 160 to 190 ms (mean 175 (12)) and in those with right and left bundle branch block it ranged from 190 to 240 ms (mean 205 (11)) and from 210 to 240 ms (230 (15)) respectively ($p<0·05$ and $p<0·02$ compared with those with narrow QRS). It is concluded that VTs in patients with left bundle branch block during sinus rhythm and prolonged H-V interval have a longer QRS duration than those with narrow QRS and right bundle branch block. Thus, the presence of His Purkinje system conduction delay during VT may suggest its participation in ventricular activation during tachycardia.

### Isosorbide mononitrate by intravenous bolus administration in acute left ventricular failure

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Nitrates represent a therapeutic alternative to intravenous diuretics in the treatment of acute left ventricular failure, but isosorbide dinitrate is less convenient than diuretics as it must be given by infusion rather than bolus injection. Eleven patients with acute left ventricular failure after acute myocardial infarction were entered into an open haemodynamic study of isosorbide-5-mononitrate. All patients had clinical and radiographic evidence of left ventricular failure, confirmed by pulmonary capillary wedge pressure (PCW) > 20 mm Hg after insertion of a flow directed, thermodilution catheter into the pulmonary artery. After acquisition of baseline data, three bolus doses (5 mg) of isosorbide-5-mononitrate were given intravenously at 15 minute intervals. Mean PCW fell from 26·2 (6·8) mm Hg at control to 17·5 (8·5) mm Hg at 45 minutes ($p<0{\cdot}01$). Cardiac index fell from 2·4 (0·8) $\text{l/min-m}^2$ to 2·3 $\text{l/min/m}^2$ ($p<0{\cdot}05$) due to a fall in heart rate (103 (11) beats/min to 97 (15) beats/min, $p<0{\cdot}05$) as blood pressure, stroke volume index, stroke work index, and systemic vascular resistance were unchanged. All patients also experienced rapid symptomatic relief. These data suggest that isosorbide-5-mononitrate is a safe, convenient, and effective treatment for acute left ventricular failure when given by intravenous bolus injection.

### Planned day case Sones's technique cardiac catheterisation

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Day case cardiac catheterisation was planned in 51% (855) of 1662 patients admitted during an 11 month period up to the end of 1985. Of these, 810 (95%) underwent uneventful cardiac catheterisation with brachial arteriotomy using the Sones's technique and were discharged the same day. All patients underwent coronary angiography with or without other catheter studies. Forty five patients (5%) were required to stay in hospital; in 18 (2%) the femoral route was used in addition, nine (1%) patients had severe angina with ST changes during the procedure, five patients (0·5%) were found to have important left main stem stenosis and were kept for elective bypass operation, two (0·12%) became hypotensive but were allowed home the following day, two remained in hospital because of oozing from the brachial arteriotomy, and two could not be discharged the same day for administrative reasons. There were no infarcts or deaths. Six patients had developed new medical problems since their preadmission assessment such that they could be not catheterised as day cases. The remaining patients were unsuitable for day case investigation because of instability, requirement for femoral approach, or other medical or geographical reasons.

Day case cardiac catheterisation improves cost efficiency and can be achieved without compromising the safety of the patient or the diagnostic sensitivity.

### Left bundle branch block: prevalence, incidence, follow up echocardiography, and exercise testing

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In a screening study of a randomly selected population of 8450 men aged 33 to 61 and 9000 women aged 34 to 61 conducted in Iceland in 1967–1977, 27 men and 17 women were found to have left bundle branch block (LBBB). In 1977 the prevalence was 0·43% in men (mean age with LBBB 58·9 years) and 0·28% in women (mean age 58·5 years). The annual incidence of LBBB was $3{\cdot}2\times10^{-4}$ in men and $3{\cdot}7\times10^{-4}$ in women. All 36 surviving patients with LBBB were examined in 1984 by chest *x* ray, echocardiography, and exercise testing (Bruce protocol). Eight men and no women had had myocardial infarction ($p<0{\cdot}05$), nine men and three women had angina pectoris, 10 women and five men had hypertension ($p<0\cdot02$, five men had cardiomyopathy, seven men and six women had primary conductive disease, two patients had complete atrioventricular block, four patients had had syncope, and three patients had pacemakers. Eleven patients were symptom free and 11 had mild and 14 had severe functional limitations. Five men and two women had died compared with 18 men and one woman in an age matched control group of 176 people (NS). Three of the five men with LBBB who died had cardiomyopathy at necropsy. Three men died suddenly. The two women died of non-cardiac causes. Only one patient in the control group had cardiomyopathy ($p<0\cdot01$). There was no significant difference in the distribution of other cardiac diagnoses between the groups. Eleven LBBB women out of 13 had an exercise test of normal duration ($\geqslant 6$ min) and 11/17 men exercised normally ($\geqslant 7$ min). Nine men and two women had an increased left ventricular diameter and three men and two women had a septal thickness of $\geqslant 1\cdot5$ cm by echocardiography. In comparison with the control group the LBBB patients had an increased left ventricular diameter 2·85 (0·38) *vs* 2·58 (0·38) cm/m$^2$ body surface area ($p<0\cdot01$) and a non-significant increase in interventricular septal thickness. There was no difference in left atrial diameter between the groups.

In conclusion, cardiomyopathy in men and hypertension in women is associated with LBBB. The prognosis of LBBB is good and few patients require pacemakers. The left ventricular diameter was increased in a randomly selected group of patients with LBBB.

## The relevance of coronary collateral flow in preserving left ventricular function

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The impact of collateral circulation of left ventricular function in response to physiological stress was determined in 50 patients at coronary angiography. Regional myocardial nutrient flow was obtained from the washout of xenon-133 at rest and immediately after maximal exercise. Fifty five collateral distributions were identified in 41 patients with coronary artery disease, of which 25 were seen angiographically and 30 by xenon-133 alone. Nutrient flow increased in response to exercise in 13 angiographic collaterals (43·7 (3·4) to 66·6 (8·5) ml/100g/min, $p<0\cdot005$) and 11 "collaterals" seen with xenon (30·2 (7·9) to 57·5 (9·3) ml/100g/min, $p<0\cdot005$). Regional left ventricular function, measured by percentage shortening, was preserved in these patients (mean 38·9 (3·9)%). Flow was maintained on exercise in six angiographic collateral distributions (45·7 (5·3) and 44·7 (6·3) ml/100g/min) and nine xenon collaterals (39·0 (7·6) and 38·4 (3·3) ml/100g/min), as was regional left ventricular function 38·8 (4·0)%. In six collaterals seen angiographically flow fell after exercise from 50·3 (7·6) to 35·3 (7·4) ml/100g/min ($p<0\cdot01$), and in 10 xenon distributions it fell from 47·5 (6·4) to 24·7 (5·9) ml/100g/min ($p<0\cdot01$). In comparison with distribution where flow increased or was maintained on exercise (percentage shortening 38·8 (2·8)%), in regions where collateral flow fell, regional left ventricular function was impaired (25·6 (2·8)%, $p<0\cdot01$). Thus, collateral flow which is maintained on exercise appears to be of value in preserving regional left ventricular function.

## Percutaneous balloon dilatation of right ventricular outflow tract and pulmonary valve in patients with tetralogy of Fallot

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Percutaneous balloon dilatation is successful in the treatment of isolated pulmonary valve stenosis and pulmonary artery branch stenosis. This encouraged us to perform percutaneous balloon dilatation of the right ventricular outflow tract and pulmonary valve in 21 symptomatic patients (aged 12 days to 18 years) with tetralogy of Fallot between December 1983 and December 1985. Eleven patients were infants under one year of age (group I). Before balloon dilatation two patients needed prostaglandin infusion to maintain ductal patency, five suffered cyanotic spells, and four had persistent severe cyanosis. After balloon dilatation palliative operation was obviated in 10 patients and the remaining patient required a Waterston anastomosis. Of the ten older patients (group II), exercise tolerance was improved and cyanosis reduced in three and hypoxic spells were abolished in one. The remaining six patients were not significantly improved. Balloon dilatation was well tolerated by all patients. One patient from group I and five from group II have subsequently had open heart surgery. The operative findings relating to the pulmonary valve were: commissural splitting in three, a flail anterior cusp in two, and a central tear of the right pulmonary cusp in one.

This preliminary report suggests that balloon dilatation in patients with tetralogy of Fallot can be performed safely; it may obviate the need for palliative surgery but is of limited use in older patients.

## Doppler echocardiographic determination of flow from five cardiac locations: a comparison with thermodilution

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In patients without intracardiac shunts or valvar insufficiency, measurement of flow from several intracardiac locations would increase confidence in values obtained by non-invasive Doppler echocardiography. The purpose of this study was to correlate volume flow, estimated from five cardiac sites by range gated pulsed Doppler techniques, with simultaneous thermodilution flow measurements. Nineteen patients, 17 men and two women, aged 35–65 (mean 50·6) years, all with ischaemic heart disease and undergoing coronary arteriography, were studied. Ascending and descending aorta, main pulmonary artery, mitral and tricuspid inflow areas were interrogated for optimal Doppler signals. Vessel and valve orifice dimensions were obtained directly from cross sectional echocardiographic images. Doppler velocity signals were obtained from the ascending aorta in 19 patients (100%), from descending aorta in 18 (95%), pulmonary artery in 12 (63%), from triscuspid inflow in 12 (63%), and from mitral inflow in 18 (85%) patients. Velocity signals from all five sites were obtained in nine patients (47%). Significant correlations with thermodilution were obtained from ascending ($r=0·69$) and descending ($r=0·72$) aortic and pulmonary artery ($r=0·65$) derived flows. The poorest correlation resulted from using mitral and tricuspid orifice derived flows.

This study demonstrates that Doppler derived aortic and pulmonary flows correlate well with thermodilution flow measurements. When quantifying intracardiac shunts or valvar insufficiency by Doppler techniques, atrioventricular valve derived flow should be avoided.

## Identification of anatomically and functionally severe coronary artery disease by the ST segment/heart rate slope

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To test the ability of the exercise ST segment/heart rate slope (ST/HR slope) to identify anatomically and functionally severe coronary disease, 84 consecutive patients with stable angina referred for coronary angiography were prospectively evaluated by a treadmill protocol designed to produce small heart rate increments between stages. The ST/HR slope, partitioned at 6 μV/beat/min in accord with previous studies, identified three vessel disease with a sensitivity of 94% (31/33) and a specificity of 63% (32/51). When three vessel disease was not present, steep ST/HR slopes identified otherwise important obstruction. Among patients with coronary disease, the anatomical extent of obstruction assessed by Gensini score was significantly greater in 47 patients with ST/HR slopes $>6$ than in 25 patients with slopes $<6$ (65 (5) *vs* 25 (4), $p<0·0001$). This was not explained by the greater number of obstructed coronary arteries found in patients with higher ST/HR slopes since among 39 patients with only one or two vessel disease the mean Gensini score was also higher in patients with slopes $>6$ (56 (8) *vs* 24 (4), $p<0·0002$). In addition the mean exercise induced fall in ejection fraction determined by radionuclide cineangiography in 36 patients was significantly greater in patients with slopes $>6$ (−7 (2) *vs* −1 (2)%, $p<0·05$). These data demonstrate that an ST/HR slope $>6$ μV/beat/min is a highly sensitive means of identifying three vessel coronary disease and that this partition value accurately identifies additional patients with angina who have anatomically or functionally extensive coronary obstruction.

## False positive ST segment depression during post-myocardial infarction exercise testing

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Electrocardiographic ST segment depression during exercise tests after myocardial infarction (MI) sometimes does not correlate with the location of coronary artery narrowing and the myocardium in jeopardy. Such ST depression is commonly termed false positive ST depression. No systematic study of false positive ST depression during post-MI exercise tests has been reported. Ninety patients with a positive 12 lead predischarge exercise test after acute MI had coronary angiography six to 12 weeks after discharge. ST segment depression in discrete ECG groupings was used to predict individual vessel disease. Twenty eight patients displayed false positive ST depression, that is no important stenosis of the suspected coronary artery. Of these, 15 had exercise induced ST elevation in the infarcted area and 15 had true posterior infarction (five were common to both groups), indicating that in these 25 patients the ST depression observed could be explained by the reciprocal electrical phenomenon. The remaining three patients had no identifiable reciprocal ST changes, but the suspect vessels all donated large collaterals to the infarcted zone suggesting a coronary steal phenomenon. During follow up (mean 12 months) those with false positive ST depression had fewer cardiac events (37% *vs* 87%, $p < 0{\cdot}05$), including angina (37% *vs* 87%, $p < 0{\cdot}05$) and further myocardial infarction (0% *vs* 18%, $p < 0{\cdot}05$) than those with true positive exercise tests. In conclusion, false positive ST depression was common during post-MI exercise tests, and may be explained by reciprocal ST changes and/or the coronary steal phenomenon. Such patients had a better prognosis compared with those who had a true positive exercise test.

## The significance of ST segment depression in syndrome X assessed by ambulatory pulmonary artery pressure monitoring

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The pathophysiology and clinical importance of anginal chest pain with a positive exercise test and normal coronary arteriography (syndrome X) are poorly understood. The purpose of this study was to determine the relation between chest pain, ST segment depression, and changes in left ventricular function assessed by the measurement of ambulatory pulmonary artery diastolic pressure (PADP) with simultaneous frequency modulated ECG in patients with syndrome X. The PADP was measured during treadmill exercise and throughout ambulatory 24 hour monitoring in unrestricted subjects; six patients with syndrome X (mean age 48 (12) years) were compared with six controls (mean age 39 (7) years) and 19 patients with coronary artery disease (mean age 57 (11) years). On treadmill exercise in both syndrome X and in normal controls there was no signficant rise in PADP despite ST segment depression (range 1–4·5 mm) in the former group. In coronary artery disease, however, on exercise there was a rise in PADP of a median 5 mm Hg (range 0–13·6 mm Hg). In only one patient with coronary artery disease was there no rise in PADP, despite 1 mm ST segment depression. During ambulatory monitoring in patients with syndrome X, 12 episodes of ST segment depression (1 mm) were observed (four painful, eight painless) in which there was no change in PADP. This differs from 29 anginal episodes in coronary artery disease in which there was a significant ($p < 0{\cdot}01$) rise in PADP of a median 7 5 mm Hg (range 1·8–19·7 mm Hg). Chest pain and ST segment changes in patients with syndrome X do not appear to be associated with impaired left ventricular function assessed by ambulatory pulmonary artery pressure monitoring. This differs markedly from the haemodynamic changes during myocardial ischaemia in coronary artery disease.

## Diurnal variation in pulmonary artery diastolic pressure: a mechanism for early morning myocardial ischaemia

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Patients may present with angina pectoris in the early morning. The mechanism of this is unclear and both haemodynamic changes and coronary artery spasm may be important. The purpose of this study was to investigate the diurnal variation in pulmonary artery diastolic pressure (PADP), reflecting left ventricular end diastolic pressure (LVEDP), in five normal subjects (mean age 39 (6·6) years), 18 patients with coronary artery disease (CAD) (mean age 57 (11) years), five patients with coronary artery spasm (mean age 51 (8) years), and six patients with syndrome X (mean age 48 (12) years). Ambulatory 24 hour recordings of PADP were obtained with a transducer tipped catheter and a simple recording system and were related to the timing of episodes of ST segment depression and elevation by simultaneous frequency modulated ECG recording. This system avoids the problems of a zero reference point commonly found with fluid filled catheters and external transducers. Episodes of ST segment change occurred predominantly in the early morning (4–8 am) in coronary artery spasm (seven out of 14 episodes), whereas in syndrome X all episodes occurred during the daytime, and in coronary artery disease painful and painless episodes were distributed throughout the day with 15 out of 67 occurring between midnight and 8 am. In all groups a similar diurnal variation in PADP was observed with a tendency for low values during the day and higher values at night with the maximum values occurring between midnight and 6 am. These findings that pulmonary artery diastolic pressure and therefore LVEDP are greatest in the early morning may suggest a new mechanism for the increased susceptibility to myocardial ischaemia during these hours.

## The effect of $\beta$ receptor antagonist therapy on the diagnostic accuracy of non-invasive tests used in the detection of coronary artery disease

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Exercise testing and ambulatory ST segment monitoring are used in the assessment of patients with coronary artery disease. These investigations are often performed while patients are taking antianginal agents but their reliability during treatment with $\beta$ blockers is unknown. The effects of $\beta$ blockade were investigated in 34 patients with coronary artery disease who had positive exercise tests and episodes of ambulatory ST segment depression while they were not on antianginal medication. After $\beta$ blockade 17 patients had no ambulatory ST segment changes (sensitivity reduced to 50%). In the remaining 17 patients the frequency, duration, and magnitude of ST segment change, whether painful or painless, were significantly reduced ($p<0{\cdot}01$). Mean exercise duration was increased by 73% ($p<0{\cdot}01$) with $\beta$ blocker treatment. Exercise tests became negative in only two patients after $\beta$ blockade (sensitivity 94%). Before $\beta$ blockade 70% of patients with three vessel disease ($n=20$) developed a positive exercise test within the first stage of treadmill exercise on the modified Bruce protocol; after $\beta$ blockade only 17% of this group of patients had positive exercise tests at this stage.

Thus the administration of $\beta$ blockers reduces the sensitivity of both exercise testing and ambulatory ST segment monitoring in the detection and evaluation of coronary artery disease. However, the effects on ambulatory ST segment monitoring are much more profound.

## Symptom limited exercise and respiratory gas exchange in heart failure

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It has been suggested that measurement of ventilatory capacity and gas exchange can be helpful in the assessment of cardiac impairment. In many subjects with heart failure exercise capacity is limited not by breathlessness but by fatigue which may vary according to the protocol—for example the speed and inclination of the treadmill. The purpose of this study was to investigate the effects of two different exercise protocols on symptoms and gas exchange when they were tested in random order in 20 patients (age 58 (11) yr) with heart failure due to left ventricular dysfunction (NHYA class II-III). The slow test had two minute stages at 1 mph/0%, 1·5/0, 1·5/4, 2/4, etc, and the fast test had one minute stages at 1/0, 1·5/4, 2/8, etc. Exercise time was 681 (233) s for slow and 289 (70) s for fast tests ($p<0{\cdot}001$). Ventilation (46 (14) *vs* 54 (13) l/min; $p<0{\cdot}001$), respiratory rate (29 (6) *vs* 32 (6) breaths/min; $p<0{\cdot}02$), heart rate (125 (20) *vs* 131 (18) beats/min; $p<0{\cdot}005$), and systolic blood pressure (143 (28) *vs* 154 (38) mm Hg; $p<0{\cdot}01$) were all higher at peak exercise with the fast test, as were maximal oxygen consumption (14·4 (5·5) *vs* 16·4 (5·0) ml/kg/min; $p<0{\cdot}005$) and respiratory exchange ratio (1·06 (0·21) *vs* 1·17 (0·17); $p<0{\cdot}005$). Anaerobic threshold was reached in only 11 patients with the slow test but in 18 with the fast test. But when only the results of the tests in those attaining the anaerobic threshold were compared the above differences were maintained. With the fast test 17 subjects stopped with breathlessness as the principal symptom compared with eight on the slow test ($p<0{\cdot}01$). The use of a single standard exercise protocol to assess cardiorespiratory function for patients with heart failure of differing severities may be inadequate. In particular anaerobic threshold will not be achieved in about half the patients during a slow protocol, and this will lead to a considerable underestimation of their exercise capacity.

## Mechanisms of closure of perimembranous ventricular septal defects: a cross sectional and pulsed Doppler echocardiographic study

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Pathological and surgical studies have shown that spontaneous closure of defects encroaching on the membranous ventricular septum (perimembranous) is less frequent than those in the muscular septum, but that there is a tendency for a good proportion of them to diminish in size, with complete closure occurring in some of them. However, the actual mechanism responsible for the partial or complete closure of these defects remains controversial. In this study the incidence and the various mechanisms involved in closure have been documented by cross sectional echocardiography and pulsed Doppler echocardiography.

Eighty five successive patients (aged from one day to 25 years) with perimembranous defects, defined by cross sectional echocardiography were studied. The age range of these patients is as follows: <1 year, 16; 1 to 5 years, 22; 6 to 10 years, 30; 11 to 16 years, 7; >16 years, 10. Thirty four (40%) of the defects showed some evidence of closure, with 28 being trabecular, three inlet defects, none in the outlet septum, and three of the confluent type. The anatomical structures responsible for the reduction in size or closure of these defects are (*a*) subtricuspid valve apparatus (24/34 cases, 70%), (*b*) bridging of septal tricuspid leaflet across the defect (7/34 cases, 20%), and (*c*) prolapse of the aortic leaflet (3/34 cases, 9%). In none of the cases was aneurysm of the membranous septum noted. Pulsed Doppler echocardiography showed systolic flow turbulence across the residual defect from left to right ventricle in all cases in (*a*) and four of seven cases in (*b*). Turbulence was noted both in the right atrium and right ventricle because of the bridging tricuspid septal leaflet across the defect. In three of seven of this group no flow was detected as the defect was completely closed by the septal tricuspid leaflet. In (*c*) all cases had evidence of aortic regurgitation as shown by diastolic flow turbulence.

From this attempt to analyse the incidence, mechanisms of closure, and residual flow jets in perimembranous ventricular septal defects by cross sectional echocardiography and pulsed Doppler echocardiography it is concluded that the tricuspid valve apparatus is the most important anatomical structure for the closure of these defects. Aneurysm of the membranous septum did not occur in this series.

## Left ventricular structure and function in bodybuilders

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Isometric exercise is known to induce cardiac muscle hypertrophy as well as skeletal muscle hypertrophy. Bodybuilding has the unique aim of inducing muscular enlargement and definition per se rather than of improving strength. It might also be expected to induce more cardiac enlargement than other isometric exercise. In addition, the use of anabolic drugs is widespread among bodybuilders, but little is known of their cardiac effects. Eighteen male bodybuilders and nine matched controls were studied by cross sectional echocardiography. Nine of the bodybuilders used anabolic drugs. The athletes were found to have significantly greater posterior left ventricular wall and septal thickness than controls, and left ventricular mass values were higher than previously reported for any athletes. In addition their left ventricular volumes were increased and ejection fractions were significantly reduced. The bodybuilders who used anabolic drugs had higher values than those who did not; but the only significant difference was for posterior wall thickness. Exercise induced cardiac hypertrophy is believed to mirror skeletal muscle hypertrophy and may be augmented by the use of anabolic drugs. In the presence of commonly used high calorie atherogenic diets there is a potential for the development of early cardiac ischaemia.

## Acromegalic heart disease: clinical features and results of treating the acromegaly

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The clinical features and prognosis of acromegalic heart disease remain ill-defined. Fifty eight (23%) of 256 acromegalic patients referred to one centre had heart disease diagnosed because of the presence of cardiomegaly, abnormal electrocardiogram, or arrhythmia. In 10 (4%) of them acromegaly was the sole cause. In the remaining 19% hypertension, ischaemic and rheumatic heart disease, and thyrotoxicosis contributed, and the diagnosis was of secondary cardiac disease. Eight of those with acromegalic heart disease had left ventricular dilatation and hypokinesia (ejection fractions 24–46%), two showed concentric hypertrophy and high ejection fractions, one with a mid-cavity gradient. Coronary arteriograms, which were performed in seven cases, showed no obstructions, but the coronary arteries were large in three. Acromegaly was cured by pituitary surgery or radiotherapy or both in six patients who were followed up for 1–11 (mean 9) years. Left ventricular function has improved in only two, deteriorated in two, and in one the gradient has resolved. Four have developed new arrhythmias but none has died of heart disease after cure of acromegaly. Cure was not achieved in four; one has been lost to follow up and three have died of cardiac failure 1–5 years after detection of heart disease.

The manifestations of acromegalic heart disease are not consistent and most cardiac disease in acromegaly stems at least partly from associated conditions. Cure of acromegaly can retard or reverse heart disease, particularly muscle dysfunction, but is often too long delayed.

## Haemodynamic function over five years after orthotopic cardiac transplantation

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The annual haemodynamic investigations following orthotopic cardiac transplantation have been reviewed from January 1980. Numbers of patients from 1–5 years were 91, 33, 18, 6, and 3. Age at transplantation ranged from 14–56 years and seven were female. Immunosuppression was achieved using prednisolone and azathioprine in 14 or using cyclosporin and azathioprine with minimal or no steroids in 77. Nine late deaths occurred, eight of whom had steroid based immunosuppression. Resting haemodynamics for the group were right atrial (mean) 5·8(4) mm Hg; right ventricular systolic 28(7) mm Hg; RV end diastolic pressure 6 3(3) mm Hg; pulmonary arterial (mean) 18·3(5) mm Hg; RR interval 697(118) ms; left ventricular ejection fraction 69·3(16·6)%; pulmonary capillary wedge pressure (mean) 11·5(5) mm Hg; left ventricular systolic 132(23) mm Hg; LV end diastolic pressure 11·3 (6) mm Hg; aorta (mean) 102(20) mm Hg; cardiac output 5·4(1·21)/min. None of these variables showed a significant trend over five years. Cyclosporin treatment was associated with hypertension (aorta mean 102(20) *vs* 92(15)) and longer RR interval (725(120) *vs* 635(96) ms). Left ventricular end diastolic pressure tended to be higher in patients with lower ejection fractions, and those with over four episodes of rejection had worse left ventricular function than those with less than four episodes. Late deaths were associated with a reduction of ejection fraction and a rise of left ventricular end diastolic pressure. All had coronary disease at necropsy. Long term haemodynamic function after orthotopic cardiac transplantation requires prevention of acute and chronic rejection and appears independent of the method of immunosuppression.

## Determinants of survival after repair of total anomalous pulmonary venous drainage

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Between June 1971 and April 1985, 28 patients underwent repair of total anomalous pulmonary venous drainage (TAPVD). The mean age at operation was 4 months (range 8 days to 1 year). Fifteen (54%) children were <3 months old. There were 22 males and six females, ranging in weight from 2·2 to 7·4 kg (mean 4·4 kg). Twelve (43%) patients had supracardiac, six (21%) intracardiac, five (18%) infracardiac, and five (18%) mixed TAPVD. Obstruction was present in 39% (11/28). Infants with obstructed TAPVD had a mean weight at operation of 3·4(0·65) kg and were operated on at a mean age of 1·43(1·9) months compared with a mean weight of 5·1(1·4) kg and a mean age of 5·8(3·7) months in the group with non-obstructed TAPVD. The overall operative mortality was 21% (6/28). The mortality was highest in (*a*) those aged <3 months of age, (*b*) those weighing <3 kg, (*c*) those with RV/LV ratio >1·0, and (*d*) in those with obstructed TAPVD. During a mean follow up of 55 months (range 6–144 months) there were two (7%) late deaths. All the survivors are symptom free, growing normally, and on no medication. Ten patients have undergone repeat cardiac catheterisation between two months and 11 years after operation. The pulmonary artery peak systolic pressure decreased from a preoperative mean of 64(35) mm Hg to 30(11) mm Hg postoperatively. There was no evidence of late pulmonary venous obstruction. Left ventricular function was normal in all the patients. Multivariate analysis showed that the strongest determinants of survival were sex, weight at operation, and pulmonary artery peak systolic pressure with age, anatomical type, presence of obstruction, RV/LV ratio, preoperative aortic saturation, and the year of operation having no significant influence on outcome.

### Accelerated graft coronary arteriosclerosis after cardiac transplantation: can it be diagnosed non-invasively?

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Severe coronary artery stenosis (CAS) due to diffuse intimal thickening is one of the potentially serious late complications of cardiac transplantation. Because of denervation angina does not occur; thus the development of reliable methods for detection of ischaemia in the transplanted heart is essential. In this study, several methods were assessed including stress testing, 24 hours ST segment monitoring, thallium scintigraphy, and radionuclide angiography. CAS was demonstrated at routine annual coronary arteriography and/or necropsy in 21 (19·8%) of 106 patients one or more years after cardiac transplantation. Eleven of these patients (group A) and 39 recipients with normal coronary arteriograms (group B) were studied. The mean (SEM) duration of treadmill exercise was 8·6 (1·52) min in group A and 10·6 (0·46) min in group B; HR × BP was 21540 (3377) and 25184 (4973) respectively; ST change <1 mm was observed in each group. In the 11 patients with CAS, thallium scintigraphy showed reversible ischaemia in one, a fixed defect in two, and normal perfusion in the remainder and in group B. Twenty four hour analysis showed transient 2 mm ST depression in one patient with CAS. Resting left ventricular ejection fraction by radionuclide angiography was 51·1 (4·64)% in group A increasing on exercise by 8·46 (2 48)%, compared with 62·1 (1·76)% and 12·3 (0·16)% respectively in group B. In conclusion, stress testing and ST segment analysis are not sensitive methods for detection of CAS after cardiac transplantation, whereas abnormal thallium scintigraphy and a resting ejection fraction <55% are suggestive of this important late complication.

### Sudden death in patients with supraventricular tachycardia terminating pacemakers

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PASAR 4151 (Telectronics) is an automatic fully implantable device which is designed to terminate tachycardia by the introduction of one or two premature beats. Worldwide 122 were implanted for the control of supraventricular tachycardia—70 for atrioventricular reentrant tachycardia (AVRT), 42 for AV nodal reentrant tachycardia (AVNRT), and 10 for other tachycardias. Over a total follow up period in excess of 2500 patient months there have been four sudden deaths: (*a*) a girl (aged 13) with Wolff-Parkinson-White syndrome (WPW) type A (refractory period, 270 ms) and orthodromic AVRT (193 beats/min) treated with two ventricular premature beats; (*b*) a woman (aged 52) with WPW type A (refractory period, 260 ms) and orthodromic AVRT (200 beats/min) terminated by two ventricular premature beats; (*c*) a man (aged 69) with ischaemic heart disease and AVNRT (170 beats/min) terminated with two atrial premature beats (coronary sinus); (*d*) a young girl with AVNRT (190 beats/min) and a nodoventricular connection treated with double right atrial stimulation. In this last patient Holter ECG recording at the time of death demonstrated seemingly spontaneous initiation of atrial fibrillation with a rapid, preexcited ventricular response (up to 375 beats/min). The role of PASAR was not apparent. The occurrence of sudden death has been unacceptably high. Possible associations include: WPW syndrome, short anterograde refractoriness of the accessory pathway, ischaemic heart disease, ventricular pacing, and the use of two premature beats, all of which should be avoided when considering the use of a pacemaker to terminate tachycardia.

### Place of antiarrhythmic therapy in acute myocardial infarction?

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Coronary care unit policy in 1974, when antiarrhythmic treatment was regularly prescribed, was compared with policy in 1984 when in general it was no longer given. The in hospital mortality has remained unchanged—16% in 1974 and 15·5% in 1984. In 1974, 108 (37%) of 295 patients with proven myocardial infarction were treated with antiarrhythmic agents for ventricular extrasystoles (VES) occurring ⩾1 in 5, couplets, multifocal, or as R on T. In 1984 only 2% of patients were treated with these agents. The incidence of ventricular tachycardia has risen from 4% to 18% ($p<0\ 001$) and ventricular fibrillation from 5% to 19% ($p<0{\cdot}001$). Of the patients with ventricular fibrillation, 6% had prodromal VES in 1974 and 10% had them in 1984. The incidence of primary ventricular fibrillation was similar in 1974 and 1984 (4% and 8% respectively). The in hospital mortality in those patients with ventricular fibrillation was not significantly different (1% to 5%). Death from ventricular fibrillation was associated with left ventricular failure (80%) and tended to occur later than 72 hours after onset of symptoms (80%).

In conclusion, a change in policy in the treatment of ventricular arrhythmias has not affected in hospital mortality in patients with acute myocardial infarction, and mortality is related to failure of pump function rather than to electrical events.

## Recognition of ventricular tachycardia and ventricular fibrillation from the timings of epicardial electrograms

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Recurrent ventricular tachycardia (VT) and ventricular fibrillation (VF) are increasingly treated by implantable cardiac defibrillators capable of delivering DC shocks between two epicardial patch electrodes. A major problem with such devices is the difficulty of recognising ventricular arrhythmias, especially VF. The possibility that VT and VF could both be distinguished from sinus rhythm and from each other by epicardial signals was therefore assessed. Ten patients undergoing elective coronary artery surgery were studied. Bipolar electrograms from four epicardial (left and right ventricular apical and paraseptal) sites were recorded simultaneously for the initial minutes of normothermic cardiopulmonary bypass during control rhythm (nine sinus, one atrial fibrillation), right ventricular pacing (to simulate VT) at three pacing rates (120, 150, and 180 beats/min), and VF induced by AC current. Control heart rates varied from 65 to 130 (mean 91) beats/min. Within each control and paced rhythm the electrograms from the four sites occurred in a stable sequence, but the sequence differed between the two rhythms in eight patients. With ventricular pacing the time from first to last electrogram increased by 40 to 90 (mean 65). Varying the pacing rate did not affect this time nor the electrogram sequence. During VF, rapid irregular localised intrinsic activity was seen at all four sites, with cycle lengths ranging from 130 to 240 ms and with signal amplitudes ranging from 0·4 to >5 times those obtained during control rhythms. Complete asynchrony of the four sites was present during VF. Detection of a different sequences and timing of multiple epicardial electrograms will allow automatic recognition of VT, and complete asynchrony of the electrograms indicates the onset of VF.

## Increase in S wave amplitude during transient myocardial ischaemia

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A consistent association between exercise induced ST segment depression and an increase in S wave amplitude has been observed. To investigate this phenomenon further, 30 high quality 24 hour Holter tapes recorded in 15 patients with chronic stable angina and important coronary artery disease were analysed. Eleven patients also underwent continuous ECG recording (12 leads) along with cross sectional echocardiography during acute myocardial ischaemia induced by intravenous dipyridamole. During Holter monitoring 157 episodes of diagnostic ST depression (0·19 (0·09) mV, mean (SD)) were detected which were invariably associated with an increase in S wave amplitude (0 23) (0·14) mV), whereas no consistent change in R wave amplitude was observed. The increase in S wave usually (70% of episodes) preceded the onset of ST depression and was quantitatively related to the severity of ST depression. For the different severity subgroups of ST depression $\geqslant 0{\cdot}1$ and $<0{\cdot}2$ mV, $\geqslant 0\ 2$ and $<0{\cdot}3$ mV, and $\geqslant 0{\cdot}3$ mV, the mean increases in S wave amplitude were 0·20 (0·09) mV, 0·27 (0 14) mV, and 0·32 (0·11) mV respectively (analysis of covariance, $p<0{\cdot}01$). Fourteen episodes of an isolated increase in S wave amplitude without diagnostic ST depression occurred; two of them were associated with angina. During dipyridamole induced ischaemia all 11 patients developed transient regional wall motion abnormalities which were associated with diagnostic ST depression (0·15 (0·02) mV) and angina in nine and with an increase in S wave amplitude in all.

It is concluded that (*a*) an increase in S wave amplitude is consistently associated with acute myocardial ischaemia; and (*b*) in some cases changes in S wave could be more sensitive than classic ST segment variables for detecting acute myocardial ischaemia.

## Epicardial repolarisation mapping in man

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Dispersion of repolarisation has been postulated as a mechanism of arrhythmogenesis, but methods for its measurement in man have remained inadequate. A new technique of epicardial repolarisation mapping is described. Monophasic action potentials were recorded intraoperatively by a specially designed hand held silver/silver chloride electrode applied to the epicardium. Recordings were obtained during fixed rate atrial pacing from 53 epicardial points. For each epicardial position activation time, repolarisation time, and action potential duration were determined. Repolarisation maps were plotted in four patients without a history of arrhythmias or myocardial infarction who were undergoing coronary bypass grafting. The number of points giving acceptable stable recordings varied between 21 and 38 in different patients. The dispersion of repolarisation times was 86 (9) (mean (SD)) ms. Repolarisation time correlated significantly with action potential duration (mean correlation coefficient, $\bar{r}=0{\cdot}67$), but not with activation time ($\bar{r}=0{\cdot}23$). An inverse relation was observed between activation time and action potential duration ($\bar{r}=0{\cdot}54$), reducing the observed dispersion of repolarisation times.

In conclusion, the technique of epicardial monophasic action potential recording offers considerable promise as a means of studying the role of repolarisation abnormalities in arrhythmogenesis in man. Preliminary observations in a small number of patients without a history of arrhythmias have shown an inverse relation between activation time and action potential duration. This may reduce dispersion of repolarisation and may represent a protective mechanism.

## Influence of R wave amplitude and Q waves on exercise induced ST segment depression

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Conflicting results have been obtained from recent studies in which the precise depth of ST segment depression during exercise has been used to predict the arteriographic severity of coronary artery disease (CAD). However, these studies have largely overlooked the influence of R wave amplitude or Q waves on ST depression. In this study 114 patients with CAD were subgrouped, firstly according to the presence or absence of Q waves and secondly according to the greatest R wave amplitude in their resting ECG. As assessed by a myocardial scoring technique the arteriographic severity of CAD was slightly greater among 26 patients with Q waves than among 88 patients with no Q waves; however, the mean maximum depth of ST depression during exercise testing was 41% greater in patients with no Q waves (1·66 (0·92) mm *vs* 1·18 (0·97) mm, $p<0{\cdot}05$). The influence of R wave amplitude was even more striking. Thirty four patients had tall (≥20 mm) R waves, 52 had medium sized (13–19 mm) R waves, and 28 had small (≤12 mm) R waves. The mean myocardial scores were similar in the three groups, the small R wave group having the highest score. However, the tall R wave patients exhibited twice the depth of ST depression seen in small R wave patients (2·04 (0·95) mm *vs* 1·03 (0·80) mm, $p<0{\cdot}0005$); whereas the medium sized R wave patients showed an intermediate amount of ST depression (1·51 (0·88) mm). Similar maximum heart rates were achieved by all five subgroups analysed.

Because of the influence of R wave amplitude and Q waves ST segment depression alone would not be expected to predict the severity of CAD.

## External non-invasive temporary cardiac pacing

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S Ikram, R Vincent, D A Chamberlain
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Transcutaneous cardiac pacing, introduced by Zoll in 1952, has attracted a resurgence of interest because longer stimulus duration and larger electrodes now permit lower stimulation thresholds. The usefulness of the Pace Aid (pulse width 20 ms, output 50, 100, or 200 mA; Cardiac Resuscitator Corporation) and the Zoll NTP non-invasive temporary pacemaker (pulse width 40 ms, output 0–140 mA; Simonsen and Weel) has been assessed. Transcutaneous pacing was attempted in 46 patients (age range 17–84)—14 with stable complete heart block, 10 with severe bradycardia and hypotension, and 22 with asystole. Transcutaneous pacing restored output in 11 patients—six with stable complete heart block, four with bradycardia and hypotension, one in asystole. In four patients the Zoll NTP created artefacts after the pacing stimulus that resembled a QRS complex but were not associated with a repolarisation wave or cardiac output. This simulates electromechanical dissociation and can cause delay in initiation of traditional resuscitation methods. External pacing was uncomfortable for conscious patients and none was able to tolerate maximal electrical output, even after intravenous sedation. A rise in pacing threshold over the course of an hour with a loss of capture was noted in one patient. Transcutaneous pacing may occasionally restore cardiac output in patients with severe bradycardia. But it proved disappointing with asystole and unreliable and uncomfortable in conscious patients with stable bradycardias. It is of limited value in the treatment of cardiac emergencies.

## Left ventricular false tendons in man: identification of clinically significant morphological variants

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Left ventricular false tendons are composed of Purkinje fibres and are intracavitary branches of the peripheral conduction system of the heart. Their clinical importance is unknown. Their morphological variation in 167 unselected diseased hearts was examined at necropsy and in 2004 consecutive patients examined by cross sectional echocardiography. Left ventricular regions were defined as apical, mid-ventricular, or basal. False tendons arising and inserting within the same ventricular region were classified as transverse, between two adjacent regions as diagonal, and traversing all three regions as longitudinal. False tendons were identified in 29 hearts (17%) in the necropsy group and in 81 patients (4%) in the echocardiographic group. Relative prevalences in the necropsy and echocardiographic groups respectively were: apical transverse (2 and 32), mid-ventricular transverse (12 and 21), apical/mid-ventricular diagonal (4 and 9), and mid-ventricular/basal diagonal (19 and 23). No longitudinal false tendons were noted. Echocardiography underestimated the occurrence of these structures which were usually an incidental finding. However, the largest clinical subset comprised 17 patients, 10 presenting with atypical chest pain and murmur and 7 with asymptomatic murmur, in whom the presence of false tendons was the only echocardiographic feature noted. This association was highly significant ($p<0{\cdot}001$). Thirteen of this group exhibited transverse morphology, with mid-ventricular location predominating ($p<0{\cdot}01$). This morphological variant, lying perpendicular to the left ventricular outflow tract, is particularly subject to traction and by disturbing intracardiac flow patterns may result in this clinical presentation.

## Characterisation of the normal right ventricular pressure-volume loop using biplane ventriculography and simultaneous high fidelity pressure measurement

A N Redington, M L Rigby, M E Hodson, P J Oldershaw
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To characterise the normal right ventricular (RV) pressure-volume (P-V) loop, biplane right ventriculography with simultaneous high fidelity pressure recordings were performed in adult patients considered to have a normal RV and normal coronary arteries at cardiac catheterisation and angiography. RV volume was measured by a modification of Simpson's rule. To validate this method of RV volume measurement, 22 radioopaque casts from necropsy human and animal right ventricles were made. The calculated volume (Vc), determined from hand digitised frontal and lateral "ventriculograms" of the casts, was compared with true volume (Vt) measured by fluid displacement. Excellent correlation was obtained after adjustment of Vc by the regression equation $Vt=0{\cdot}86\,Vc+0{\cdot}68$ ($r=0{\cdot}99$, SEE (4)). Frame by frame analysis of right ventriculograms obtained at catheterisation thus enabled the generation of a simple volume-time curve from which the P-V loop was derived. Fundamental differences were found between normal RV and left ventricular (LV) P-V loops. The normal RV P-V loop was more triangular in shape with ejection beginning during pressure upstroke. Consequently there was no well defined period of isovolumic contraction. Furthermore RV volume continued to decrease well beyond peak RV pressure, up to 60% of the stroke volume being ejected during RV pressure fall. These differences may reflect the low impedance to pulmonary flow.

In conclusion, the normal RV P-V loop was significantly different from that of the normal LV; this observation has important implications when considering isovolumic or end systolic indices of RV contractility.

## Phase and amplitude analysis of exercise digital left ventriculograms: a new method of detecting myocardial ischaemia

J Lyons, M Norell, J Gardener, R Balcon, C Layton
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Phase and amplitude analysis of digital left ventriculograms allows assessment of wall motion while avoiding the artefacts associated with image subtraction. Intravenous digital left ventriculography was performed in 23 patients with known coronary artery disease (CAD): eight with one vessel disease, 11 with two vessel disease, and four with three vessel disease. Images were obtained at 12·5 frames/s in a right anterior oblique projection after a right atrial injection of contrast. Patients then performed a symptom limited supine bicycle exercise test. A second ventriculogram was obtained at peak exercise. The resultant images were subjected to phase and amplitude analysis, and assessed blindly in random order, with the ventricle considered as three segments. All ventricles were found to be abnormal at rest, despite normal cineangiograms in eight patients. In all but one, the wall motion abnormalities were consistent with the CAD. On exercise, five patients showed no change in wall motion; all had one vessel disease. In 13 patients there was a deterioration in wall motion affecting a previously normal segment in six and an abnormal one in seven; this group contained all four patients with three vessel disease and six with two vessel disease. In five patients, all with two vessel disease, there was either a discrepancy between the abnormal segments at rest and on exercise, or apparent improvement in wall motion of one segment.

Phase and amplitude analysis of digital left ventriculograms is a method of assessment of exercise induced ischaemia that is simple to perform, has high resolution, and is a sensitive detector of severe CAD.

## Plasma catecholamine secretion during cardiac surgery: a double blind comparison of trimetaphan camsylate with sodium nitroprusside

Laura Corr, R M Grounds, J G Whitwam,
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Cardiopulmonary bypass has been shown to be a potent stimulus to the release of catecholamines and may be associated with a high systemic vascular resistance. Furthermore the concentrations of circulating plasma catecholamines reported may have important metabolic effects. The effects of trimetaphan camsylate (TC) and sodium nitroprusside (SNP) on the catecholamine response to cardiac surgery were compared in a randomised, double blind study of 12 male patients undergoing elective myocardial revascularisation. The solutions were titrated to maintain a mean arterial pressure of 70–85 mm Hg before and after bypass and <70 mm Hg during bypass. The rise in plasma adrenaline in the SNP group during cardiopulmonary bypass (0·019 (0·007) ng/ml to 1·058 (0·228) ng/ml) was much greater than in the TC group (0·018 (0·007) ng/ml to 0·261 (0·136) ng/ml; $p < 0·02$ between groups). There was a smaller rise in plasma noradrenaline in the SNP patients (0·482 (0·098) ng/ml to 2·933 (0·8) ng/ml) but this was significantly higher than in the TC patients (0·484 (0·16) ng/ml to 1·286 (0·511) ng/ml; $p < 0·05$ between groups). The plasma potassium and glucose concentrations in the two groups were also compared. Plasma potassium fell initially on bypass in the SNP group (4·34 (0·08) to 4·0 (0·16) mmol/l) but did not fall in the TC group (4·23 (0·15) to 4·20 (0·18) mmol/l). Thereafter plasma potassium tended to rise in both groups but remained lower throughout operation in the SNP patients ($p < 0·02$). Plasma glucose rose in the TC group (to 6·53 (0·21) mmol/l) but the rise in SNP group was significantly higher (to 9·48 (0·82) mmol/l; $p < 0·05$ between groups).

The use of TC provides a simple and effective way to reduce catecholamine release during cardiopulmonary bypass. The haemodynamic benefits of vasodilation are obtained and the metabolic consequences of high circulating catecholamines are avoided.

## Free radical generation in coronary and peripheral vascular disease

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Oxygen free radicals (FR) may be important mediators of tissue damage in pathological states involving inflammation and ischaemia. Methods to assess changes in the cell defence to free radical generation have been developed—such as measurement of glutathione concentration and superoxide dismutase activity. Raised concentrations of glutathione and decreased concentrations of superoxide dismutase correlate with increased free radical generation. Glutathione and superoxide dismutase were measured in 26 patients with arterial disease and the results compared with those in 17 matched controls. Superoxide dismutase concentrations were significantly lower in patients with arterial disease (48 (7) μg/ml in patients with angina ($p<0·02$), 44(6) μg/ml in patients with claudication ($p<0·01$)) than in normal individuals (71 (5) μg/ml). In contrast glutathione concentrations were significantly raised—270 (32) μg/ml in patients with angina ($p<0·01$), 292 (30) μg/ml in claudication ($p<0·04$), 208 (17) μg/ml in controls. All patients with angina had important double or triple vessel disease and positive exercise tests. There was no significant change in superoxide dismutase and glutathione concentrations during exercise induced myocardial ischaemia.

These results suggest that these markers of excessive free radical production may define patients with vascular disease affecting the coronary and peripheral circulation.

## $^{31}$P nuclear magnetic resonance evaluation of skeletal muscle metabolism during exercise in congestive heart failure

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In patients with congestive heart failure (CHF) the severity of exercise intolerance correlates poorly with central haemodynamic abnormalities. This suggests that the pathophysiology may be due to alterations in skeletal muscle metabolism or muscle blood flow. To study the mechanism of exercise impairment in CHF, we performed $^{31}$P magnetic resonance spectroscopy (MRS) in nine male patients (aged 42–62) with CHF due to ischaemic cardiomyopathy (6) and primary myocardial disease (3). Their mean ejection fraction was 16 (3)% and their maximum exercise tolerance ranged from 25 to 100 W. A 1·89 tesla, 20 cm bore magnet operating at 32·5 MHz for $^{31}$P was used with a surface coil over the flexor digitorum superficialis muscle. A previously standardised exercise protocol was used in which patients squeeze a rubber bulb at a rate of 22/min against a pressure of 100 torr for 5 min, followed by 300 torr for 2·5 min. Serial 32 scan spectra were obtained at 1·2 min intervals and analysed for pH, phosphocreatine (PCr), and inorganic phosphate (Pi). The rate of phosphate utilisation was followed as the ratio of PCr:(PCR + Pi).

Compared with 18 controls (aged 20–80) the CHF patients had similar resting pH (7·00 (0·03)) and PCr ratios (0·88 (0·03) *vs* 0·90 (0·02)). During exercise pH fell more rapidly in the patients and remained lower (6·40 (0·27) *vs* 6·86 (0·10) at 100 torr, $p<0·001$; 6·44 (0·21) *vs* 6·68 (0·23) at 300 torr, $p<0·02$). The PCr ratio fell faster at 100 torr (to 0·33 (0·15) *vs* 0·49 (0·14), $p<0·02$) but at 300 torr reached a comparable level albeit with more work from the controls. Unlike the controls, five of the nine CHF patients developed double Pi peaks indicating the presence of at least two populations of muscle fibres with differing metabolic responses to exercise. These findings indicate that in CHF patients, skeletal muscle exhibits metabolic abnormalities during exercise which may be consistent with impaired nutritive blood flow or intrinsic alterations in cellular energetics.

## Biochemical changes during repeated occlusion and reperfusion of a coronary artery in the rabbit: a $^{31}$P magnetic resonance spectroscopy study

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Recanalisation of occluded coronary arteries is now an established therapeutic manoeuvre but the metabolic effects of reperfusion of the ischaemic myocardium are less well understood. We used $^{31}P$ magnetic resonance spectroscopy (MRS) to follow serially the metabolic effects of repeated myocardial ischaemia and reperfusion in six anaesthetised ventilated open chest rabbits. A 16 mm surface coil was placed on the lateral surface of the left ventricle and an adjustable snare was placed round a branch of the left coronary artery. Spectra were obtained in an Oxford Instruments 1·89 tesla 20 cm bore magnet. Changes in phosphocreatine (PCr), ATP, and inorganic phosphate + 2–3 diphosphoglycerate were measured from peak areas and pH from the chemical shift of inorganic phosphate. Spectra were obtained during a control period, during 15 min of total occlusion of the coronary artery, and after reperfusion. After allowing 45 min for recovery, the protocol was repeated. After occlusion, PCr fell rapidly in the first 7·5 min to 69% of control and remained depressed for the remaining ischaemic period. The pH fell from control to between 6·3–6·5. The ATP did not change for the first 7·5 min, but fell to 90% of control during the second 7·5 min. When the vessel was reperfused, PCr returned to 103% of control within the first 10 min. In two animals ATP showed partial recovery, but in four it remained depressed or fell further. Arterial blood pressure fell by 10% during ischaemia and showed recovery to near control values after reperfusion. The peak areas immediately preceding the occlusion were used as control values and the magnitude and time course of changes after the second occlusion were similar to those that followed the first occlusion.

Unlike perfused hearts, in this in vivo model of regional ischaemia PCr fell precipitously to be followed by a fall in ATP. During reperfusion, PCr recovered while ATP remained depressed or fell further in four animals. This loss of ATP may contribute to the loss of function seen after repeated periods of ischaemia (the stunned myocardium). In summary, it is possible to follow serially the metabolic changes in repeated periods of ischaemia, and this should allow the study of models of reperfusion injury and pharmacological interventions.

*Br Heart J* 1986; 55: 529

# *Correspondence*

## Lead specificity of the maximum ST/heart rate slope response

Sir,

We are disturbed that correspondence regarding the maximum ST segment/heart rate slope[1] remains focused on the issue of test perfection[2] rather than on the potential value and limitations of this method.[3] Since no diagnostic test of this type can be wholly accurate, demonstration of test imperfection[4 5] is predictable. But does this mean that further study of a potentially important contribution to exercise electrocardiography should be abandoned?

Surely a more important question is whether this method can improve the predictive accuracy and clinical usefulness of the exercise electrocardiogram. In patients with stable angina we have found that a modified ST segment/heart rate slope analysis can significantly improve our ability to identify patients with anatomically and functionally severe coronary artery disease.[6 7] Indeed a similar conclusion regarding identification of three vessel disease might be drawn from the data of Quyyumi *et al*.[4] The study by Balcon *et al* unfortunately included only two patients with three vessel disease.[5]

The failure of some studies to reproduce the test accuracy reported from Leeds should not stop further study of the method but rather should raise important and answerable questions about the optimal applicability of the ST segment/heart rate slope in different clinical populations. Although the test can be highly accurate for the detection of three vessel disease in patients with stable angina pectoris, the method is inaccurate shortly after transmural infarction and does not predict the severity of coronary disease in patients with aortic regurgitation.[3] Test inaccuracy is also likely in the various cardiomyopathies. Heterogeneity of study populations may thus explain some of the controversy surrounding the ST segment/heart rate slope. In addition, selection and referral patterns may also affect test accuracy in patients with angina.[8] These are interesting and resoluble problems that require investigation. As these data accumulate is it not reasonable to suggest that careful definition of study populations might further clarify the clinical usefulness and limitations of the method?

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*Br Heart J* 1986; 55: 530

# *Notices*

## British Cardiac Society

The Autumn Meeting will be held at the Wembley Conference Centre, London, on 25 to 27 November 1986, and the closing date for receipt of abstracts will be 1 August 1986.

## Lasers in cardiovascular diseases

The 1st International Symposium on Lasers in Cardiovascular Diseases will be held in Baden (near Vienna) on 26 to 28 June 1986. Further information from: The Secretariat, 1st International Symposium on Lasers in Cardiovascular Diseases, c/o Interconvention, PO Box 80, A-1107 Vienna, Austria.

## Nuclear cardiology

The European Society of Cardiology Working Group on Nuclear Cardiology will be holding a symposium in Edinburgh from 6 to 8 May 1987. Further details from: Congress Secretary—Edinburgh '87, Cardiac Department, St Bartholomew's Hospital, London EC1A 7BE.

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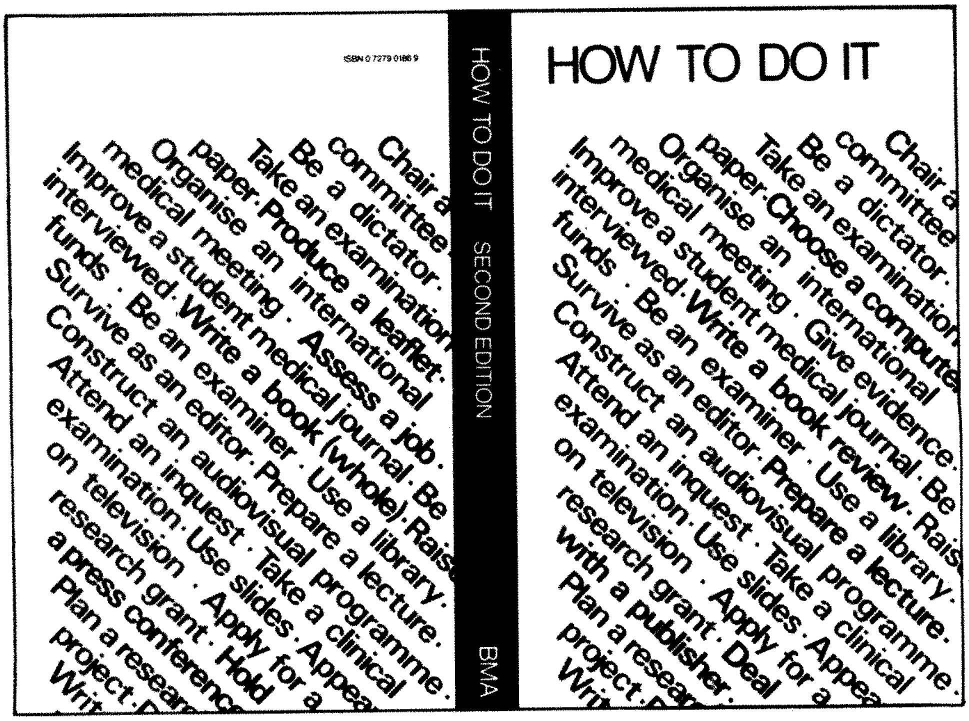
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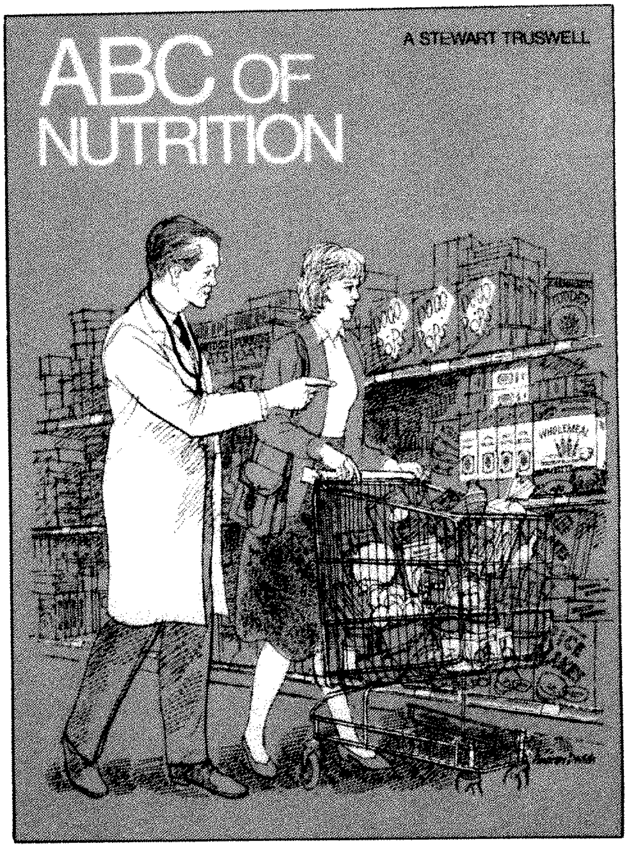

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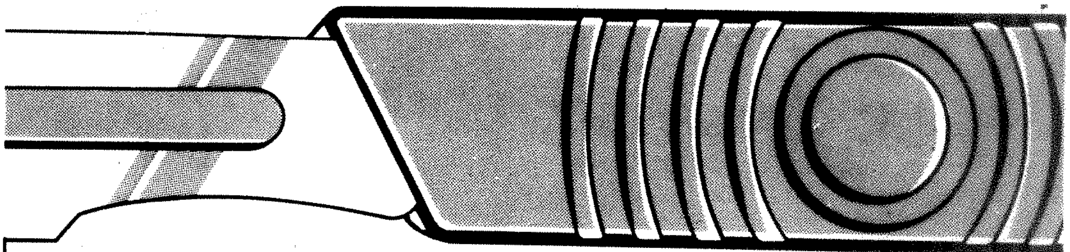

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Published by British Medical Association, Tavistock Square, London WC1H 9JR
and printed in England by Eyre & Spottiswoode Ltd, Thanet Press, Margate.

**Prescribing Notes for 'Kalten' and 'Tenormin' LS**

### DOSAGE

**Hypertension** 'Kalten' – 50mg atenolol + 25mg hydrochlorothiazide + 2.5mg amiloride hydrochloride (as amiloride hydrochloride BP 2.84mg) orally one capsule daily, recommended where monotherapy with beta-blocker or diuretic proves inadequate.
'Tenormin' LS – 50mg atenolol orally once a day; some patients may respond adequately to 'Tenormin' low strength (LS).
**Children** – 'Kalten' and 'Tenormin' LS are not recommended for use in children.
**Elderly patients** – Dosage requirements for 'Tenormin' LS may be lower, especially in patients with renal impairment.
'Kalten' may be suitable for older patients where higher doses of the constituents are considered inappropriate.

### CONTRA-INDICATIONS

'Kalten': Heart block, hyperkalaemia, anuria, acute renal failure, severe progressive renal disease, diabetic nephropathy, blood urea over 10mmol/l or serum creatinine over 130 micromol/l if not possible to monitor carefully and frequently. In renal impairment additional potassium conserving agents may cause hyperkalaemia. Sensitivity to hydrochlorothiazide or amiloride hydrochloride.
'Tenormin' LS : Heart block.

### PRECAUTIONS

Untreated cardiac failure, bradycardia, renal failure, anaesthesia, pregnancy. Disturbed fluid or electrolyte balance. Caution in patients with chronic obstructive airways disease or asthma. Atenolol modifies the tachycardia of hypoglycaemia. Co-administration with verapamil or Class I antidysrhythmic agents.
Withdrawal of clonidine.
Withdrawal of beta-blocking drugs should be gradual in patients with ischaemic heart disease.
**Additional precautions for 'Kalten'**
Co-administration with lithium.
**Metabolic effects:** Measurement of potassium levels is appropriate, especially in the older patient, those receiving digitalis preparations for cardiac failure, taking abnormal (low in potassium) diet or suffering from gastrointestinal complaints.
Caution in metabolic or respiratory acidosis.
**Diabetes:** 'Kalten' may lower glucose tolerance. Discontinue before glucose tolerance testing. Hyponatraemia and hypochloraemia may occur.
**Hepatic or renal impairment:** Caution in patients where fluid and electrolyte balance is critical. Hyperkalaemia and hypokalaemia may occur. Discontinue treatment if increasing azotaemia and oliguria occur.
Amiloride may precipitate hepatic encephalopathy. Jaundice may occur in cirrhotic patients.
**Breast-feeding:** Discontinue if 'Kalten' deemed essential.

### SIDE-EFFECTS

Coldness of extremities, bradycardia and muscular fatigue may occur. Sleep disturbance rarely seen. Rashes and dry eyes have been reported with beta-blockers – consider discontinuance if they occur.
With amiloride hydrochloride and hydrochlorothiazide gastrointestinal disturbances may occur. Side-effects commonly associated with diuresis; dizziness and headache may occur. Skin rashes and blood dyscrasias have been reported.

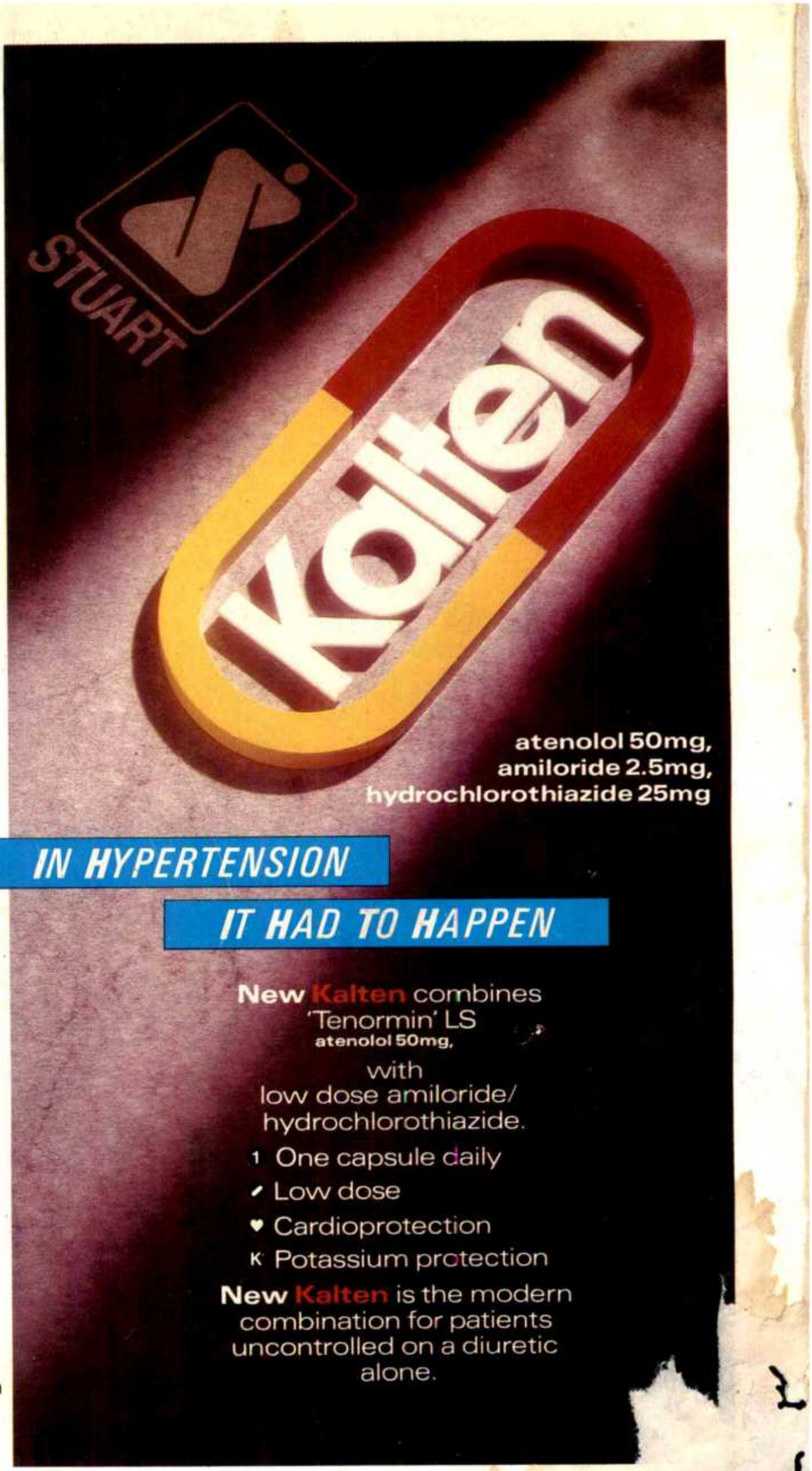
### PRODUCT LICENCE NUMBERS AND BASIC NHS COST

'Kalten' Capsules 29/186 in calendar packs of 28, £6.70.
'Tenormin' LS Tablets 29/86 in calendar packs of 28, £4.88.

'Kalten' and 'Tenormin' LS are trade marks.

Further information is available on request from the Company.

STUART
**Stuart Pharmaceuticals Limited**
Stuart House, 50 Alderley Road,
Wilmslow, Cheshire SK9 1RE.



**atenolol 50mg,**
**amiloride 2.5mg,**
**hydrochlorothiazide 25mg**

## IN HYPERTENSION
## IT HAD TO HAPPEN

**New Kalten** combines
'Tenormin' LS
**atenolol 50mg,**
with
low dose amiloride/
hydrochlorothiazide.

- 1 One capsule daily
- ✓ Low dose
- ♥ Cardioprotection
- K Potassium protection

**New Kalten** is the modern combination for patients uncontrolled on a diuretic alone.